INTRODUCTION

The current state of health care is inextricably linked with the focus on evidence-based medicine, the main directions of which are: standardization of health care and medical research, active use of decision support systems in medical research, development of clinical reference systems.

The rapid development of medical and biological sciences observed over the past 100 years, the rapid increase in information about the causes, pathogenesis, prevention and treatment of various diseases, on the one hand, has contributed to the progress of health care, and on the other hand, has caused complications in the objective assessment of numerous phenomena arising in the human body under the influence of pathogenic and therapeutic factors.

Suffice it to note that the number of indicators describing the functional state of the body, which should be used by doctors and researchers, has increased more than 40 times over the past 70 years, and the number of therapeutic interventions has increased by more than 100 [54]. This led to the need for a narrow specialization of doctors, the creation of research centers with a strict direction of pathology treatment, a noticeable increase in the field of medicine, an increase in the cost of treatment, and an increase in the terms of care. The effectiveness of the analysis of the growing flow of diagnostic and therapeutic information has significantly decreased. Moreover, the fate of drug subjectivism (already inherent in medicine) in the process of diagnosis, prediction of the consequences of the disease and the choice of treatment method has significantly increased. Overcoming the contradictions between the volume of medical information and the possibility of its full-fledged analysis is possible with the use of information systems in medicine based on methods of modeling, system analysis and decision theory.

At the same time, the basis for decomposition in the algorithms of system analysis in medicine is the meaningful model of the disease. The disease means the integration of pathological processes, which is characterized by the limitation of

protective and adaptive phenomena and a decrease in human performance [61]. Hence, the study of the pathological process should be decisive in the analysis of the disease.

The history of biological and medical cybernetics dates back to the first half of the 60s. It was then that in the works of P.K. Anokhin on the study of auxiliary reactions of the body and N.A. Berstein in the field of physiology [9], the foundations and methods of a systematic approach in the field of physiology, which are fully cybernetic, were developed. In the early 1970s, the definition of the subject and method of biocybernetics according to M.M. Amosov [4] and A.B. Kogan [54] appeared. Thus, M.M. Amosov believes that biological cybernetics is a direction of cybernetics that studies the general laws of storage, processing and transmission of information in biological systems [3] [5-7, 9, 14, 26, 49, 51, 53, 54, 57, 59, 63, 77, 101, 106, 107, 120].

At the same time, the widespread introduction of information technologies and methods into medical science and practice, just as it happens in technology, economics, the financial industry and even ecology, requires the emergence of new convenient algorithms for the construction and analysis of mathematical models in classes of nonlinear functional-differential equations and their implementation in the form of appropriate software environments with user-oriented interfaces.

Significant results in this direction were achieved in the Ukrainian School of Cybernetics and Informatics, created by V.M. Glushkov [47, 74]. An important contribution to the development of the theory and methods of system analysis, mathematical modeling and optimization, general control theory, as well as to the development of appropriate software tools in Ukraine was made by G.M. Bakan, I.V. Beiko, B.M. Bublik, F.G. Garashchenko, O.Y. Gryshchenko, V.Y. Danilov, M.Z. Zgurovsky, M.F. Kyrychenko, V.M. Kuntsevich, O.G. Nakonechnyi, O.M. Novikov, Y.M. Onopchuk, B.N. Pshenichnyi, I.V. Sergienko, Y.I. Samoilenko, A.O. Chikriy, Y.M. Yermoliev, V.O. Yatsenko and others.

Fundamental and applied results have been obtained on the issues of process forecasting and decision-making in complex systems with incompleteness, inaccuracy and fuzziness of initial data under conditions of conceptual uncertainty [12, 13, 16, 43-48, 56, 110-112]; analysis and optimal control of processes and fields of various nature [18, 31, 39, 71-73]; theory of differential games [68, 82]; numerical methods of nonlinear analysis and optimization [17, 18]; theories of infinite-dimensional dynamical systems [35]; methods for evaluating and controlling nonlinear systems with distributed parameters [18].

The vast majority of processes in medicine are complex non-linear. This includes the complexities associated with aftereffect effects. A variety of random perturbations (noises) that make processes stochastic should also be taken into account. The very formulations of medical problems are inherently the tasks of studying the stability, sensitivity, and controllability of dynamic systems.

This paper proposes an approach to the construction and analysis of models of system medical research in classes of balance models, functional-differential equations, which are called population dynamics equations. Models of population dynamics belong to the class of the oldest nonlinear dynamical systems encountered by researchers [131], and today have proven themselves in the study of ecological systems [51, 57], a number of problems of immunology and epidemiology [51, 53, 54, 9]. The paper systematically introduces the equations of population dynamics for pathological processes of the human body. This made it possible to develop a Web-integrated software environment for supporting systemic medical research.

Relevance of the topic. In the vast majority, medical scientific research in the field of pathological processes offers statistical indicators for diagnosing and evaluating the effectiveness of therapeutic and preventive measures. Such approaches sin linearity, the results obtained are suitable only for justifying existing treatment regimens and can be applied to specific pathologies and narrow groups of patients.

These shortcomings can be eliminated by considering the pathological process as a dynamic system, the model of which contains the equation of population dynamics for pathogenic factors and protective and adaptive reactions of the body.

The expediency of such work lies in the development of accurate diagnostic methods and optimal schemes of therapeutic and preventive measures – one of the main principles of evidence-based medicine, the direction chosen by the health care of Ukraine.

Connection of work with scientific programs, plans, topics. In 1998, the World Health Organization adopted the document "Policy for Achieving Health for All in the XXI Century". In accordance with it, the Intersectoral Comprehensive Program "Health of the Nation" was developed in Ukraine. Its tasks are to strengthen the health of the population, preserve working capacity, improve the demographic situation in the state and increase the efficiency of health care.

The basis for this work was the comprehensive research work of the Central Research Laboratory of the Ternopil Medical University on the topic "Structural and functional substantiation of magnetolaser exposure for the prevention and correction of colon lesions" (state registration number 0101U001312), which was carried out by order of the Ministry of Health of Ukraine.

Purpose of the study. The purpose of the work is to develop mathematical methods for system analysis of pathological processes in the class of equations of population dynamics, as well as to implement them in the software environment for supporting systemic medical research.

Research objectives:

a) to build mathematical models for the damaging effect of the pathogenic factor and pathological and protective and adaptive reactions, to study the existence and uniformity of solutions of such equations;

b) to solve the problems of a posteriori minimax estimation of parameters, which in the general case are functions;

c) calculate equilibrium states and obtain the conditions of stability, asymptotic stability, instability in classes of equations of population dynamics;

d) to propose ways to find solutions to functional-differential equations of population dynamics in an explicit form;

e) to make mathematical formulations of problems of controlling pathological processes, to propose conditions of controllability and ways to build optimal control both explicitly and by numerical methods;

f) to propose ways to classify the forms of pathological processes based on models of population dynamics;

g) to investigate the conditions for the occurrence of bifurcations and chaos in models of pathological processes both by analytical methods and by means of numerical characteristics of nonlinear dynamics;

g) to develop a conceptual model of the software environment for supporting systemic medical research;

h) to propose a model of publication in the field of systemic medical research and implement it in terms of appropriate software tools;

i) to develop a program interface of the environment that will be Web-integrated, user-oriented, and has modification capabilities;

i) to implement mathematical methods of system analysis of pathological processes in the form of a hierarchy of program classes;

j) to develop software tools for performing research, preparing the results obtained for publication on the Internet and their visualization.

The object of study is a pathological process as a set of pathological and protective-adaptive reactions that occur in response to the damaging effect of a pathogenic factor [61].

The subject of the study is models of population dynamics, which will be consistently applied to the modeling and analysis of pathological processes.

Research methods. Deterministic mathematical models were used to describe pathological processes. At the same time, phase coordinates, which are the numbers

or densities of populations of certain cells, describe the corresponding average values. The pathogenic factor was described by the differential equations of generalized dynamics of Gompertz. The immune status of the organism was described by the model of the immune system of G.I. Marchuk. The resourcefulness of immune defense mechanisms was described by logistic equations. groups of cells (leukocytes), to describe the density of which integro-differential models were used. When identifying the parameters of the above models, which are generally elements of the Hilbert space, the methods of minimal posteriori estimation and the estimation method based on sensitivity functions were used. The stability of compartments of the pathological process model was studied by the method of studying stability by the first approximation, as well as by the method of Lyapunov functionals. To obtain the general solution of a linear system with a constant delay, the method of integral transformations was used. The controllability conditions for Gompertz dynamics models are obtained using finite control methods. When solving the problem of choosing optimal therapy modes, the Pontryagin maximum principle was used for the problem with phase restrictions. Studying the occurrence of the Hopf bifurcation in the model of immune defense of G.I. Marchuk, the properties of the quasipolynomial of the fourth order were used, and the finding of the periodic solution was carried out by the method of decomposition by a small parameter. The study of the nonlinear dynamics of the pathological process was carried out using the analysis of phase portraits, as well as through numerical characteristics: autocorrelation, maximum Lyapunov exponent, correlation dimension.

Scientific novelty of the results obtained. The dissertation presents new theoretical data on the ways to solve the problem of creating mathematical methods of system analysis of pathological processes in the class of equations of population dynamics, as well as their implementation in the form of a software environment for supporting systemic medical research.

The results of the work made it possible to obtain methods for building models, identifying their parameters, as well as analyzing the stability,

controllability and nonlinear behavior of trajectories for pathological processes, as well as to develop appropriate software tools.

For the first time, a generalized model of the tumor process was developed in the class of Gompertz dynamics equations. Unlike previously known results that do not distinguish between subpopulations of tumor cells, the model describes populations of proliferating, clonogenic and normal cells, while isolating different resistance to n cytotoxic agents.

Integro-differential models of populations that "do not know" the exact value of the maturation period of individuals have been improved due to the introduction of the memory function.

For the first time, a model of the pathological process was built as a result of aggregation of models for the pathogenic factor, the immune system, and the resourcefulness of the mechanisms of the cellular link of immune defense.

The methods of a posteriori minimax estimation were further developed in the work. Namely, they were developed into differential equations with Voltaire operators with parameters in Hilbert space. Such problems arise when identifying models proposed to describe pathological processes.

The theory of analytical solutions of differential equations for equations with a delay has been developed. By introducing the concept of a delayed exponent for the first time, it was possible to write down the general solution of linear differential equations with a constant delay in an explicit form.

For the first time, control for Gompertz dynamics in the class of generalized functions was constructed, and design conditions of controllability for a number of specific sets of permissible controls were obtained.

When solving the problem of choosing optimal therapy regimens with the use of two cytotoxic agents, which is a control problem with phase constraints, the concept of an integral exponential order function was introduced for the first time α, which is a generalization of the well-known Euler function. This made it possible

to obtain constructive conditions of optimality, which in certain cases are reduced to checking the compatibility of the system of algebraic inequalities.

By studying the placement of the roots of a quasipolynomial of the fourth degree, for the first time, the condition for the occurrence of Hopf bifurcation in the model of the immune system due to a change in the amount of delay was obtained. Unlike the previous results obtained in numerical form, this condition is formulated in terms of system coefficients. When studying bifurcations in the model of the pathological process, traditional numerical characteristics were also calculated. At the same time, the method of calculating the maximum Lyapunov exponent through the renormalization procedure has been improved.

Practical significance of the results obtained. The methods of system analysis developed in this paper have been brought to computer implementation. A Web-integrated information-control system for supporting systemic medical research has been developed, which has been implemented in the scientific work of the Ternopil Medical University (Appendix B.1). At the same time, for the first time, a model for presenting the results in the field of systemic medical research based on XML technology has been proposed. and an open library of relevant Java classes. The use of certified Java applets in the environment significantly weakens the requirements for its hardware and software support. The demo version of the software environment is available upon request.

Mathematical methods of system analysis of models based on nonlinear functional-differential equations of population dynamics are implemented in the computer program "INTEGRA-POST" (Appendix B.2), which contains basic classes of the software environment of system medical research.

A mathematical model of the state of bone tissue has been developed, which is implemented in the computer program "Prognosis Bone Tissue" (Appendix B.1) and implemented in the treatment of patients with acute and chronic hemoblastosis in a number of medical institutions (Appendices B.6-B.18).

The model of toxic colitis developed in this work and its computer implementation was used for the structural and functional substantiation of magnetolaser exposure for the prevention and correction of colon lesions and in the study of the features of the small and large intestine in combined pathologies of the pancreato-hepatobiliary zone (Appendix B.4).

In the educational process at the Department of Disaster Medicine and Military Medicine of the Ternopil State Medical Academy named after I.Y. Horbachevsky, the study of the procedure for developing complex software complexes on the example of the software environment developed in this work (Appendix B.2) has been introduced.

In the material of the course of lectures of the Department of Pathological Physiology of the Ternopil Medical University, the teaching of methods of system analysis proposed in this work in the study of diseases that are not modeled on animals (Appendix B.3) is introduced.

The results of the systematic analysis of pathological processes were used to determine the biological age of a person based on the indicators of biological markers in the development of the computer program "BIOAGE" (Appendix B.3), implemented at the Department of General Hygiene and Ecology of the Ternopil State Medical Academy named after I.Y. Horbachevsky (Appendix B.5).

Personal contribution of the applicant. When developing an algorithm for applied system analysis of the study of the pathological process, Lisnychuk N.E. and Baraniuk I.O. proposed the decomposition of the content model of the pathological process. All other results of Section 1 were obtained by Martsenyuk V.P. personally. The problem statements of Section 2 belong to Nakonechnyi O.G. Martsenyuk V.P. introduced the methods of minimax posteriori estimation to their solution. Zhulkevych I.V. Ideas for building a logistic model of bone mineral density tissue (BMD) and the connection of the BMD with the height of the PVC vertebrae. In Chapter 3, Kovalchuk O.Y. calculates the exponential quasipolynomial in G.I. Marchuk's model of immune defense. In Chapter 4, D.Y. Khusainov has the idea of

a delayed exponent. All other calculations and studies were performed by V.P. Martsenyuk personally. In Section 5, R.B. Ladyka and O.Y. Kovalchuk performed the calculation of optimality conditions. The idea of an integral exponential function of a certain order and its application to the principle of maximum belongs to Martsenyuk V.P. Nakonechnyi O.G. proposed a condition for checking optimality for various kinds of control sets and using the method of finite control. All other results on the construction of controllability conditions belong to V.P. Martsenyuk personally. Semenets A.V., Sverstiuk A.S. and Vakulenko D.V. participated in the development of a software environment for supporting systemic medical research, presented in Chapter 7. The concepts of such an environment and the choice of software tools and algorithms belong to V.P. Martsenyuk.

Approbation of the results of the dissertation. The results of the research included in the dissertation were reported: at the Taras Shevchenko National University of Kyiv at the seminar "Modeling and Optimization of Dynamic Systems" (supervisors – Prof. Nakonechnyi O.G., Prof. Garashchenko F.G.), at the Institute of Cybernetics named after V.M. Glushkov of the National Academy of Sciences of Ukraine at the seminar of the Department of Functional Information Systems (supervisor – Prof. Y.M. Onopchuk), at the National Technical University of Ukraine "Kyiv Polytechnic Institute" at the seminar of the Physics and Technology Institute. Institute (head – Prof. O.M. Novikov). They were also published at scientific forums: IV Crimean International Mathematical School "Lyapunov Method of Functions and Its Application" (Alushta, 1998), International Conference "Dynamical Systems Modelling And Stability Investigation" (Kyiv, 1999), V Crimean International Mathematical School "IFF - 2000" (Alushta, 2000), International Conference on Management "Automatics - 2000" (Lviv, 2000), International Conference "Differential and Integral Equations" (Odesa, 2000), Conference on Differential Equations and Dynamical Systems (Lisbon, 2000), International Workshop "Control Applications of Optimization" (St. Petersburg, 2000), International Conference "Modeling and Optimization of Complex Systems"

(Kyiv, 2001), III Moscow International Conference on Operations Research (ORM2001) (Moscow, 2001), Fifth Mississippi State Conference on Differential Equations & Computational Simulations (Mississippi, 2001), International Conference "Dynamical Systems Modelling and Stability Investigation" (Kyiv, 2001), International Conference "Differential Equations and Nonlinear Oscillations" (Chernivtsi, 2001), International Workshop "Problem of Decision Making and Control Under Uncertainties (PDMU-2002)" (Kaniv, 2002), II International Scientific and Practical Conference "Information Technologies in Health Care and Practical Medicine" (Kyiv, 2002), IV International Scientific and Practical Conference of Students, Postgraduates and Young Scientists "System Analysis and Information Technologies" (Kyiv, 2002), VI Crimean International Mathematical School "Lyapunov's Method of Functions and Its Application" (Alushta, 2002), International Scientific and Practical Conference of Students, Postgraduates and Young Scientists "Computers. Program. Internet. 2003" (Kyiv, 2003), V International Scientific and Practical Conference of Students, Postgraduates and Young Scientists "System Analysis and Information Technologies" (Kyiv, 2003), International Conference "PDMU-2003" (Alushta, 2003), International Scientific Conference "Sixth Bogolyubov Readings" (Chernivtsi, 2003), International Workshop "PDMU-2004" (Ternopil, 2004), I All-Ukrainian Scientific and Practical Conference "Medical Technologies and Higher Education" (Lutsk, 2004), 11th International Conference on Automatic "Automation-2004" (Kyiv, 2004).

Publication. The results of the work have been published in 2 monographs, in 48 articles in scientific journals, in 28 materials and abstracts of conferences, of which 27 are in professional publications recommended by the Higher Attestation Commission of Ukraine.