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NUMERICAL MODELING OF INVERSE PROBLEMS IN BIOMEDICINE AND ECONOMIC

ABSTRACT

of the dissertation in partial fulfillment of the requirements
for the degree of Doctor of Philosophy (PhD) in specialty
6D070500 – «Mathematical and computer modeling»

The relevance of research. Terms such as "inverse problem" and "ill-posed problem" have been steadily and confidently gaining popularity in modern science since the middle of the 20th century. In just over 50 years of studying such problems, it was shown that many problems in various directions of classical mathematics (computational algebra, differential and integral equations, partial differential equations, functional analysis) can be classified as inverse and/or ill-posed problems, which are the most difficult because they are unstable and usually nonlinear.

At the same time, inverse and ill-posed problems began to be studied and systematically applied in physics, geophysics, medicine, astronomy and other areas where mathematical methods are used. The reason is that the solutions of inverse problems describe important properties of the medium, including the density and speed of wave propagation, elastic parameters, conductivity, permittivity and permeability, as well as the properties and location of inhomogeneities in inaccessible regions, etc.

Recently, there has been a rapid introduction of mathematical modeling methods for solving urgent problems of biomedicine. As we know, mathematical modeling plays a huge role in research in various fields of science. In particular, the study and modeling of dynamic processes in biomedicine, in particular the modeling of the processes of pharmacokinetics, epidemiology and immunology. The practice of scientific research requires the development of new promising directions in the study and use of biomedicine processes, the expansion of the range of mathematical models under study, the creation of stable mathematical methods for solving the inverse problems arising in this case, based on the use of computer technology.

The modern development of natural sciences is inextricably linked with the development, analysis and practical use of mathematical models arising in the study of biomedicine processes. A complete description of these models or processes requires the specification of information on the number of certain constituents of the object and subject of research; in many cases, such data are not available for direct measurement and are required. A feature of inverse problems in biomedicine is finding unknown parameters in models described by ordinary differential equations based on experimental data.

It should be noted that the methods applied to solving problems of biomedical processes can also be applied to solving mathematical models of economic processes.

Thus, the relevance of the research topic is beyond doubt, it is of scientific and practical interest.

Objective: modeling and solving inverse problems in biomedicine based on identifiability, and extending this method to modeling and solving economic problems.

In connection with this goal, the following research **tasks follow**:

– A study of parameter sensitivity validation for model restructuring or parameter ordering to improve structural or practical identifiability using numerical analysis.

– Investigation of identifiability for problem of a simplified and expanded two-chamber model of C-peptide secretion for the prevention of diabetes mellitus using numerical analysis.

– Statement of an inverse problem for a two-chamber model of C-peptide secretion, its reduction to an optimization problem

– Application of the differential evolution algorithm to restore the values of the model parameters.

– Development of a universal model, with different values of the parameters, describing both the processes of biomedicine and the processes of economic growth.

– Investigation of the neoclassical economic Solow model and the optimization solution of the inverse problem of recovering its coefficients.

– Solving the inverse problem of restoring the production function at a constant and space-dependent technological level, carrying out a numerical analysis.

Object of study. The object of the study is the process of pharmacokinetics and economic growth under the influence of various parameters.

Subject of study. The subject of the research is the parameters of the biomedicine models and the economic model of Solow, along with the production function.

Research methods. The following methods of identifiability analysis were applied: Monte Carlo method, matrix correlation method and confidence interval method; differential evolution algorithm; *potterswheel* software package for constructing confidence intervals, likelihood functions and correlation matrix of parameters; AMIGO software package for identification analysis; for technical calculations in solving problems, numerical modeling and visualization of processes, the MATLAB application package was used, for parallel computations, the NKS-30T cluster in the Siberian supercomputer center was used.

The scientific novelty of the work consists in restoring the coefficients of two-chamber models of C-peptide secretion for the prevention of diabetes mellitus; in the application of stochastic optimization (differential evolution algorithm) when finding the global minimum for an immensely large matrix, which was previously impossible when using classical algorithms; in obtaining a universal model that describes both the processes of biomedicine and the processes of economic growth;

in restoring the coefficients of the modernized neoclassical economic model of Solow with the addition of human capital; in the restoration of the production function of the Solow spatial model, using modern approaches of mathematical modeling and computer visualization of the results.

Scientific positions submitted for defense:

– analysis of identifiability and verification of the sensitivity of the parameters of the mathematical model describing biomedical processes;

– restoration of the parameter values of the mathematical model of biomedicine by additional statistical information;

– application of stochastic optimization (differential evolution algorithm) when finding the global minimum for an immensely large matrix;

– a new model describing both the processes of biomedicine and economic growth;

– restoration of the values of the parameters of the mathematical model of neoclassical economic growth due to additional statistical information;

– reconstruction of a production function for the spatial Solow economic model described by partial differential equations.

The reliability and validity of scientific statements, conclusions and results of the dissertation work is confirmed by the use of systems of nonlinear ordinary differential equations, which are built on the basis of the mass balance law and work in a closed system when describing processes in biomedicine and economics and constructing mathematical models; comparison and satisfactory agreement of the results of solving inverse problems of the obtained models with their reliable analogues.

Theoretical and practical significance of the research. The theoretical significance of the work lies in the development of a new direction of identifiability of a set of parameters of a mathematical model; in the application of stochastic optimization to find the global minimum, which was previously impossible when using classical algorithms; in the development of a new universal mathematical model describing the pharmacokinetics of C-peptide and the process of economic growth; in the development of methods for their solution and analysis, generalization of the results of their research.

The practical significance of dissertation research is that the use of modern methods of mathematical modeling and computer technology brings the results obtained as close as possible to real processes, in biomedicine it makes it possible to predict the pharmacokinetics of drugs in the human body with high accuracy, in the field of economics it makes it possible to predict economic growth with the involvement of changes human capital.

The relationship of this work with other research works. The dissertation research was carried out under the grant funding program of the Ministry of Education and Science of the Republic of Kazakhstan:

– «Theory and numerical methods for solving inverse and ill-posed problems in natural science» (2015-2017 years, №1746/ГФ4);

– «Numerical methods of identifiability of inverse and ill-posed problems in natural science» (2018-2020 years, № AP05134121).

Approbation of work. The main results of the work were reported and discussed at the following events:

– IV-VII International Farabi Readings (Almaty, Kazakhstan, April 10-13, 2017, 2018, 2019, 2020).

– VI Congress of the Mathematical Society of Turkic-Speaking Countries (L.N. Gumilyov Eurasian National University, Astana, Kazakhstan, October 2-5, 2017).

– 3rd International Symposium «Mathematical Modeling and High-Performance Computing in Bioinformatics, Biomedicine and Biotechnology. (Novosibirsk, Russia, August 21-24, 2018).

– VIII international scientific and methodological conference "Mathematical modeling and information technologies in education and science" (MMITES, Almaty, Kazakhstan, October 3-4, 2018).

– Inverse Problems, Design, and Optimization Symposium – IPDO2019 (Tianjin, China, September 24-26, 2019)

– XIII international youth scientific school - conference "Theory and numerical methods for solving inverse and ill-posed problems" (Akademgorodok, Novosibirsk, Russia, August 2019).

– International scientific conference «Inverse Problems In Finance, Economics and Life Sciences» (Almaty, Kazakhstan, August 31 - September 4, 2019)

– Report at School of Science, Zhejaing Sci-Tech University (Zhejiang, China, October 25, 2019).

– "Theory and numerical methods for solving inverse and ill-posed problems", XII International Youth Scientific School - Conference (Akademgorodok, Novosibirsk, Russia, October 4-12, 2020).

– scientific seminars of the Faculty of Mechanics and Mathematics of al-Farabi KazNU (2017-2020, Almaty);

– scientific seminars of the Department of Mathematical and Computer Modeling of al-Farabi KazNU (2016-2020, Almaty).

– as part of a research group of scientists from al-Farabi KazNU on predicting the spread of coronavirus infection COVID-19 in Kazakhstan reported to the Security Council of the Republic of Kazakhstan (July-August 2020).

– Joint international scientific seminar with Middlesex University (London, UK), Institute of Computational Mathematics and Mathematical Geophysics (Novosibirsk, Russia) and al-Farabi KazNU (January 2021).

Publications. On the topic of the dissertation 11 works were published, including 4 publications in scientific journals included in the list recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan for the publication of the main results of scientific activity; 1 in a rating scientific publication indexed by Scopus and Thomson Reuters, with an impact factor of 0,926, citescore 1.7, SJR 0.501 and

procentile 48; 6 publications in the materials of international conferences, including 2 publications in the materials of foreign conferences.

Works published on the topic of the dissertation are given in the bibliography.

Structure and scope of work. The dissertation work consists of a title page, content, designations and abbreviations, an introduction, four sections, a conclusion, a list of 106 sources used. The total volume of the dissertation is 74 pages, including 20 illustrations, 15 tables and three appendixes.

The main content of the thesis. This work is devoted to the numerical modeling of inverse problems arising in biomedical processes. Before proceeding with the solution of inverse problems, it is necessary to provide identifiability analysis described in Chapter 1, which presents its basic concepts (identifiability, global, local, structural and practical identifiability) and methods for identifiability analysis, such as: Monte Carlo method, matrix correlation method and method confidence interval. Also important element is parameter sensitivity testing to help rebuild the model or reorder parameters to identify less important parameters to improve structural or practical identifiability. Thus, using Monte Carlo methods, confidence intervals and the matrix correlation method, an analysis of practical identifiability was carried out for further construction of a regularization algorithm for the numerical solution of inverse problems.

Chapter 2 presents the results of identifiability analysis for problems of a simplified and expanded two-chamber model of C-peptide secretion, presented in the form of ordinary differential equations, for the prevention of diabetes mellitus. The formulation of the direct problem is described. The *potterswheel* software package was used to construct the confidence intervals, likelihood functions, and the parameter correlation matrix for further solving the inverse problem.

In Chapter 3, an inverse problem was formulated for a two-chamber model of C-peptide secretion, which was reduced to an optimization problem. A differential evolution algorithm is applied to restore the value of the model parameters, which is an effective global optimization method for the restoration of the parameter value, which was studied and tested during a foreign scientific internship at Middlesex University, London, England. It was found that the visualization of the numerical results showed good agreement between the statistical data and the modeling data.

In the course of the research work, a universal model was derived, with the substitution of various parameter values, describing both the processes of biomedicine and the processes of economic growth, which is described in Chapter 4. Also, this chapter presents the setting of the neoclassical economic Solow model and the Menkew-Robert-Weill model (the modernized Solow model with the addition of human capital), where it was necessary to restore the parameters both in the form of ordinary coefficients and presented as a power. The neoclassical economic growth model was developed in the form of the Solow spatial model, where the solution to the inverse problem was to restore not only the coefficients, but also the production function at a constant and space-dependent technological level.