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Mathematical Methods in Biomedical Studies: The Need for New Approaches to Study of Follicular Thyrocytes

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Abstract. The current stage of medical science development requires updating the methodological and procedural base of research, which leads to the expansion of the mathematical methods' scope for medical purposes, including medical diagnosis. Most frequently, its problems are solved by Bayesian, correlation and regression analysis, phase interval method and the methodology of the logical conclusion (logical programming), which operate on quantitative information and are not designed to use qualitative and binary data. The methodology of the fuzzy-set logic, which permits to transform qualitative information into mathematical dependencies, is not widely used yet in the study of biological objects, as it assumes a rigid dependence of some phenomena on others, which is not typical of living biological systems. This limits the use of mathematical technologies to study the characteristics of changes that occur in cells of the body under the influence of various factors. To effectively solve a number of multidisciplinary medical, medico-social and social problems, namely polyetiologically caused thyroid pathology, it is necessary to develop modern informative approaches to study the activity of the thyroid gland in normal and pathology based on mathematical methods.

Keywords: biomedical diagnosis, mathematical methods of biomedical diagnosis, thyroid gland, follicular thyrocyte.

Introduction. Medical science, which is closely related to the pharmaceutical sciences [1] at the present stage of its development needs a radical renovation of methodological, procedural and organizational-legal [2-4] base: empirical data obtained using even the most modern research methods can no longer provide correct requirements for their comprehensive generalization [5]. This leads to the expansion of the scope of mathematical methods for the needs of various branches of medicine, including medical diagnosis [6]. Updating and enriching the arsenal of scientific methods requires the creation of new concepts and, consequently, fields of research [7-11]. At the same time, a number of medical, pharmaceutical, legal and medico-social issues are under close scrutiny and multidisciplinary research, as for a number of reasons they cannot be removed from the agenda and remain relevant [12-14].

Such problems include pathology of the thyroid gland (TG). The main reason for this is the importance of the thyroid gland for the body: through its hormones, it is involved in almost all vital functions [15-17]. At the same time, there is now an increase in thyroid pathology. It is believed that this is due to the hypersensitivity of the gland to various endogenous and exogenous influences, which may be microelement landscape of the residence area, features of nutrition, ionizing and electromagnetic radiation, industrial or anthropogenic pollution by chemical thyrodisraptors [18].

Currently, the main areas of the thyroid gland study continue to be the determination of hormone levels (mainly T3, T4, TTH, which indicate the functional activity of the TG), and the study of morphological changes in the organ structure in various diseases. The rationale for such research approaches is to find a better understanding of the thyroid pathology pathogenesis and to identify changes that indicate the efficacy/inefficacy of its drug therapy. However, no properties of an isolated object, which are inherent in the TG as an organ, can be studied without taking into account the properties of its constituent elements, the nature of their relationships, interactions and interinfluences. Thus, the specific activity of thyroid follicular thyrocytes occurs simultaneously in the fields of thyroid hormones synthesis, their elimination, transportation by intraorganic microcapillary bed, energy supply of these processes. However, in common scientific sources we have not found information on the use of mathematical methods that would permit to study these aspects of the TG as a hormonopoietic organ.

The aim of the study was to research theoretically the possibilities of using of mathematical methods in the thyroid cells study.

Materials and methods. The study was carried out using bibliographic databases Google Scholar, Web of Science and Scopus using Ukrainian, English, and Russian keywords: mathematical methods in medicine, Bayesian analysis, correlation analysis, regression analysis, phase interval method, logic programming, fuzzy logic. The obtained data were collected and analyzed to determine the use of mathematical methods in biomedical research.

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Results and discussion. Normal and pathological processes have a number of interrelated features of qualitative and quantitative nature, which ultimately determine exactly the way the biological system functions, which is most appropriate in terms of its structure and potential. Most qualitative biological phenomena are at the same time quantitative, which determines the possibility of their quantification. Interest in formalizing the various life processes of biological objects has grown sharply. Involvement of mathematical technologies in the analysis of data obtained during research permits to identify and explain both the laws of individual organs or systems, and their relationships and interactions, to cognize the main and intermediate stages of functioning of any biological object, which is certainly a qualitatively higher stage of its knowledge. It is mathematical analysis that helps to clearly trace the dependence of some phenomena in a biological object on others, which further permits to formulate hypotheses about the interdependence of different systems functioning of the whole living organism. For a total, modern approaches to mathematical analysis of the biological systems functioning in normal and pathology help to establish its patterns, permit to predict with high probability the consequences of various processes and expand the possibilities of the researcher’s intervention to correct pathological changes.

Any task of medical diagnosis is to find a reflection:

$$X^* = (x_1^*, x_2^*, \dots x_n^*) \rightarrow d_j \in D = (d_1, d_2, \dots d_m),$$

where X^* is the state parameters set of the studied system/organ/patient,
and D is the set of diagnoses inherent in this field of medicine.

With the development of medical science, the number of diagnostic parameters is steadily increasing, while the direct relationship between the parameters of the studied system/organ/patient and the diagnosis cannot always be traced. The difficulty of establishing such dependencies is due to the huge number of parameters of the studied biological system, and their heterogeneous nature –quantitative (age, morphometric characteristics, content of certain substances, etc.), qualitative (nature, intensity, pain location, general state, mood, etc.), binary (presence or absence of a state or process).

Problems of medical diagnostics are most frequently solved using the following mathematical methods: Bayesian analysis, correlation-regression analysis, phase interval method, method of logical programming, fuzzy set analysis.

Bayesian analysis has been implemented in various fields of research [19,21]. This approach assumes that:

if $p(d_j)$ – a priori probability of diagnosis d_j; $j = \overline{1,m}$; $P(X^*/d_j)$ – conditional probability of occurrence in a patient with state parameters $X^* = (x^*_1, x^*_2, \ldots x^*_n)$ diagnosis d_j; $P(d_j/X^*)$ – a posteriori probability of the patient's diagnosis d_j according to the presence of the vector of state parameters X^*,

then according to Bayes' theorem:

$$P(d_j / X^*) = \frac{p(d_j) \cdot P(X^* / d_j)}{\sum_{j=1}^{n} p(d_j) \cdot P(X^* / d_j)}.$$

This formula permits to list the a priori probabilities of various diseases into a posteriori probability through the X^* vector of parameters. After calculating the a posteriori probabilities of all possible diagnoses d_j, $j = \overline{1,m}$ choose the diagnosis with the highest probability. However, in medical diagnostics the application of the Bayesian approach has certain limitations. The main ones are only the use of quantitative information [22,23] and the assumption that each disease has a pathognomonic complex of symptoms. At the same time, statistical information, which is a necessary basis for the application of the method, is usually limited in practical medicine, and the introduction of new data into the model is associated with the need to recalculate all probabilities.

Regression analysis involves the use of linear regression equations.

Let q be some initial parameter, the value of which determines the diagnosis of the disease (for example, the content of thyroid hormones in the serum).

q depends on the vector of input parameters $X = (x_1, x_2, \ldots x_n)$.

In this case, you can build a linear regression equation:

$$q = a_0 + a_1x_1 + a_2x_2 + \ldots + a_nx_n \ ,$$

where q depends on the vector of input parameters $X = (x_1, x_2, \ldots, x_n)$,

whereas $a_0, a_1, a_{2,}, \ldots a_n$ are unknown parameters that are determined by the method of least squares [24,25].

One of the disadvantages of using regression analysis in medicine is the ability to solve only those problems of diagnosis and prediction in which the parameters of the patient's condition and diagnosis are quantitative [26-28]. Since the value of the initial parameter q very much depends on the experimental conditions under which the coefficients $a_0, a_1, a_{2,}, \ldots a_n$, were estimated, the models obtained under one condition do not always correspond to other conditions. In addition, in order to obtain statistically significant coefficients in the regression equations, it is necessary to process a large amount of studied material, which is not always possible in the conditions of experiment and clinic.

Correlation analysis establishes relationships between the studied parameters, the nature and severity of which is determined by the pairwise correlation coefficient [29-31]. Long-term use of the method contributed to the accumulation of data for study of various biomedical processes [32,33] at their multiple levels [34-36], which led to the development of tools to facilitate visualization, analysis and interpretation of information [37,38]. However, the method is not intended to work with qualitative or binary data on the state of the studied biological system.

Phase interval method. According to the main provisions of this method [39,40], determining the actual state of the biological system/patient to a diagnosis is possible by calculating the distance between two points in the phase space, which is E_s – Euclidean space, each coordinate $x_i (i = \overline{1,n})$ which corresponds to one of the parameters the patient's condition, while the points $(x_1, x_2, \ldots, x_n)$ of the phase space correspond to certain diagnoses d_j, $j = \overline{1,m}$. The study of medical histories of patients with correct diagnoses permits to identify in the phase space those areas (sets of points) $D_1, D_2, \ldots D_m$, that correspond to the diagnoses $d_1, d_2, \ldots d_m$. The midpoints of these regions are determined by the points $C_1, C_2, \ldots C_m$.

Let X^* be a point in the phase space that reflects the patient, and let $R(x^*, c_j)$ be the interval between the points X^* and C_j, $j = \overline{1,m}$. In this case, the diagnosis d^*_j, which corresponds to the state $X^* = (x^*_1, x^*_2, \ldots, x^*_n)$, is indicated by the point C^*_j and the area D^*_j, for which

$$R(X^*, C^*{}_j) = \min_{j=\underline{1,m}} \{R(X^*, C_j)\}\,.$$

In the E_s-space, the distances $R\ (A, B)$ between the points $A = (a_1, a_2, \ldots a_n)$ and $B = (b_1, b_2, \ldots b_n)$ are calculated or it is done by Hamming:

$$R(A,B) = \sum_{i=1}^{n} |a_i - b_i|\,,$$

or according to the Cartesian distance:

$$R(A,B) = \sqrt{\sum_{i=1}^{n} (a_i - b_i)^2}\,.$$

The phase interval method does not require the accumulation of significant statistical material and its labor-intensive processing, but its application is only limited by quantitative and binary parameters of the state of the studied biological system/patient.

The Methodology of the logical conclusion, which is implemented using the logic programming language (Prolog) [41], which is widely used in expert systems, it is advisable to use to find a chain of rules ranging from factors (x^*_i) to goal (d^*_j) or goal (d^*_j) to factors (x^*_i), selected from the database. However, Prolog solves the problem by the search method, which limits its possibilities for infinite source sets [42]. Although the method permits not only to diagnose, but also to justify the reasons for the decision, it cannot be used in cases of diagnosis in which information about the studied biological object is unclear, probabilistic in nature.

The Methodology of the fuzzy-set logic. It is used as a means of solving research problems that arise in biomedical research in the study of living organisms

[43-45]. The basis for the mathematical study of non-numerical (linguistic) information is the theory of fuzzy sets [46,47].

Let U be a universal set, i.e., a complete set that covers the entire problem field.

The fuzzy set F of the clear set U is determined by the membership function $\mu_F(u)$, where u are elements of the set U, i.e., $u \in U$.

The membership function maps elements from the set U to the set of numbers in the interval [0, 1], which indicate the degree of belonging of each element $u \in U$ of the fuzzy set $F \subset U$.

If the universal set U consists of a finite number of elements u_1, u_2, ..., u_n, then the fuzzy set F can be represented as follows:

$$F = \mu_F(u_1)/u_1 + \mu_F(u_2)/u_2 + \ldots + \mu_F(u_n)/u_n = \sum_{j=1}^{n} \mu_F(u_j)/u_j \ .$$

Fuzzy conclusions are based on fuzzy relationships. For the successful implementation of medical diagnostics on the basis of fuzzy logic [48] it is necessary to adhere to such scientific and methodological principles as the principle of linguistic diagnosis and parameters of the patient and the principle of linguistic diagnostic databases.

According to the principle of linguistic diagnosis and parameters of the patient's condition, the parameters of the patient's condition (input variables) and the diagnosis of his disease (output variable) are considered as linguistic variables with qualitative terms. A linguistic variable is a variable whose meanings are words or sentences of natural language, i.e., qualitative terms. Examples of linguistic variables and their terms in relation to the state of the thyroid gland can be as follows:

- endoplasmic reticulum (rough, smooth; narrowed, moderately pronounced, dilated; with low ribosome content, moderate ribosome content, significant ribosome content, etc.);
- mitochondriae (in reduced quantities, in moderate quantity, in increased quantities; habitual form, altered form; with degenerative changes, without degenerative changes; with a homogeneous matrix, with an inhomogeneous

matrix, etc.);

- Golgi apparatus (narrowed, moderately expressed, expanded; rich in secretory inclusions, poor in secretory inclusions, etc.);
- lysosomes (small, medium, big; insignificant electron density, moderate electron density, significant electron density, etc.);
- electronic density of cytoplasm/intrafollicular colloid (insignificant, moderate, significant);
- hypothyroidism (subclinical, moderate, significant), etc.

In these examples, the first five variables relate to the parameters of the condition, and the last one to the diagnosis. Using the concept of membership function, each of the linguistic terms can be formulated as a fuzzy set, which is given in the corresponding universal set.

According to the principle of linguistic diagnostic databases, the causal relationships between the patient's condition parameters (causes) and the diagnosis (consequence) are first described in the words of the language used. Then they are formalized in the form of a set of fuzzy logical statements, namely: “if — then, otherwise.” An example can be the characterization of the morpho-functional state of the follicular thyrocyte:

“If the shape of the cell is cubic; electronic density of cytoplasm – moderate; electronic density of colloid – moderate; microvilli of the apical cytoplasmic membrane – thick, thin, short; the number of microvilli is moderate; the amount of mitochondria is moderate; the width of the elements of the rough endoplasmic reticulum is moderate; the magnitude of the elements of the Golgi apparatus is moderate; the number of free and bound ribosomes and polysomes is moderate; the number of lysosomes is moderate; electron density of lysosomes – moderate; the number of apical secretory granules is moderate; the electron density of the apical secretory granules is moderate,

then the functional state of the thyrocyte is balanced (normal).”

The set of statements “if — then, otherwise” is considered as a set of points in the space “state parameters — diagnosis”. According to a vague logical conclusion at these points, the surface is reproduced, which permits to assess the diagnosis by such state parameters, for which information is not available in the database. Unlike traditional models, which are based on quantitative mathematics, the adequacy of fuzzy logical statements does not change under slight fluctuations in experimental conditions.

As a result of our literature search, it should be noted that mathematical methods traditionally used in biomedical research are poorly adapted to study the activity of cells, including thyroid cells, which in the process of hormonopoiesis are subject to various functional changes and transformations. This significantly limits or makes it impossible to study and interpret the features of changes that occur in the thyrocyte under the influence of various factors. However, taking into account both the shortcomings and possibilities of the considered mathematical methods of medical diagnosis for the needs of our multidisciplinary study of thyroid hormonopoiesis and interactions of the thyroid gland and other internal organs, we proposed a comprehensive using elements of regression analysis, correlation analysis and fuzzy logic, which is reflected in scientific publications [49-58].

Conclusions. An important disadvantage of the considered methods is the focus mainly on quantitative data, while qualitative and binary information, which permits to determine the smallest nuances of the biological object’s state, is ignored. The use of fuzzy logic to study qualitative/binary data implies a strict determination that is not typical of many biological systems. Since the thyroid gland is important for the body, there is an urgent need to use mathematical methods to develop modern informative approaches to the study of its activity in normal and pathology and their implementation in the practice of scientific research.

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