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:

\[ X^* = (x_1^*, x_2^*, \ldots x_n^*) \rightarrow d_j \in D = (d_1, d_2, \ldots d_m), \]

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 \( d_j \); \( j = 1, m \); \( P(X^*/d_j) \) – 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 \( d_j, j = 1, m \) 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 $x_i(i = 1,n)$ 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 $d_j, j = 1,m$. 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 $C_j$, $j = 1, m$. 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

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

In the $E_5$-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.
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 $F \subseteq U$.

If the universal set $U$ consists of a finite number of elements $u_1, u_2, \ldots, u_n$, 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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References.

1. Shapovalov V. (Jr.), Gudzenko A., Komar L. et al. Concerning the importance of forensic and pharmaceutical researches to improve patients’ accessibility to medicines. *Pharmacia*. 2017. Vol. 65. No. 2. P. 23–29. URL: [http://bsphs.org/wp-content/uploads/2017/07/Shapovalov.pdf](http://bsphs.org/wp-content/uploads/2017/07/Shapovalov.pdf).

2. Hayduchok I., Shapovalov V. Forensic pharmacy and medicine: risks for pharmacotherapy of addiction and countering of illegal circulation of psychoactive substances in the COVID-19 pandemic. *SSP Modern Pharmacy and Medicine*. 2021. Vol. 1. No. 2. P. 1–28. URL: [https://doi.org/10.53933/sspmpm.v1i2.32](https://doi.org/10.53933/sspmpm.v1i2.32).

3. Shapovalova V. The ICD-11 for the twenty-first century: the first view from the organizational, legal, clinical and pharmacological aspects. *SSP Modern Pharmacy and Medicine*. 2022. Vol. 2. No. 1. P. 1–13. URL: [https://doi.org/10.53933/sspmpm.v2i1.37](https://doi.org/10.53933/sspmpm.v2i1.37).

4. Shapovalov V. (Jr.), Zbrozhek S., Gudzenko A. et al. Organizational and legal analysis of the pharmaceutical provision for the most common diseases of society. *International Journal of Pharmaceutical Sciences Review and Research*. 2018. Vol. 51. No. 1. P. 118–124. URL: [http://globalresearchonline.net/journalcontents/v51-1/18.pdf](http://globalresearchonline.net/journalcontents/v51-1/18.pdf).

5. Avtandilov G. G. Meditsinskaya morfometriya: Rukovodstvo [*Medical morphometry: a Guide*]. Moscow: Meditsina; 1990. 384 p.

6. Slavin M.B. Metody sistemnogo analiza v meditsinskikh issledovaniyakh [*Methods of Systematic Analysis in Medical Researches*]. Moscow: Meditsina; 1989. 304 p.

7. Ryabukha O. Innovative model for studying the features of hormono-poietic cells functioning based on characteristics of different aspects in their activity (as examplified by follicular thyrocytes). In: *Scientific basis of modern medicine: collective monograph*. Boston: Primedia eLaunch, 2020. pp. 171–181. URL: [https://doi.org/10.46299/isg.2020.MONO.MED.I](https://doi.org/10.46299/isg.2020.MONO.MED.I).
8. Ryabukha O.I. Conceptual approaches to the study of the thyroid gland at different levels of its integration into the body. *Endocrinology and Disorders*. 2020. Vol. 4. Iss.1. URL: https://doi.org/10.31579/2640-1045/047.

9. Ryabukha O.I. Substantiation of conceptual apparatus for mathematical studies on the hormone-producing cell activity. *Bulletin of problems in biology and medicine*. 2018. Iss. 3. No. 1(145). P. 234–237. URL: https://doi.org/10.29254/2077-4214-2018-3-145-234-237.

10. Riabukha O. Application of new information technologies for the study of cell activity. In: *Proceedings of the XIth International Conference on Perspective Technologies and Methods in MEMS Design* (MEMSTECH); 2015 Sep 2-6; Lviv, Ukraine. New York (NY), United States: IEEE; 2015. P. 69–71. URL: https://ieeexplore.ieee.org/document/7299458.

11. Ryabukha O.I. Perspectives of applying new approaches to the implementation of mathematical technologies in the study of cell activity. *Medical Informatics and Engineering*. 2018. No. 1. P. 67–75. URL: https://doi.org/10.11603/mie.1996-1960.2018.1.8894.

12. Hayduchok I. Pharmacotherapy of psoriasis support with antiphospholipid syndrome: ABC/VEN analysis of anti-viral drugs. *SSP Modern Pharmacy and Medicine*. 2021. Vol. 1. No. 1. P. 1–12. URL: https://doi.org/10.53933/sspmpm.v1i1.4.

13. Ryabukha O. COVID-19: Multidisciplinary studies on the thyroid activity during the pandemic and post-covid processes. *Actual Problems of Medicine and Pharmacy*. 2022. Vol. 3. No. 1. P. 1–25. URL: https://doi.org/10.52914/apmp.v3i1.39.

14. Ryabukha O. COVID-19 pandemic encourages to deepen the study of the thyroid gland: correlation portraits as a means of research in different directions of follicular thyrocytes activities. *SSP Modern Pharmacy and Medicine*. 2022. Vol. 2. No. 1. P. 1–21. URL: https://doi.org/10.53933/sspmpm.v2i1.40.
15. Ishikawa A., Kitano J. Ecological genetics of thyroid hormone physiology in humans and wild animals. In: N. K. Agrawal (ed.). *Thyroid Hormone*. London: IntechOpen; 2012. pp. 37–50. URL: https://www.intechopen.com/chapters/37917.

16. Ryabukha O.I. Deyaki aspekty vplyvu shchypodobnoyi zalozy na stan orhanizmu v umovakh normy i patolohiyi [Some aspects of thyroid impact on the body state in normal and pathology conditions]. *Aktualni problemy suchasnoyi medytsyny: Visnyk Ukrayinskoyi medychnoyi stomatolohichnoyi akademiyi - Actual Problems of the Modern Medicine: Bulletin of Ukrainian Medical Stomatological Academy*. 2018. Vol. 18. No. 3. P. 324–330. URL: http://nbuv.gov.ua/UJRN/apsm_2018_18_3_69.

17. Ryabukha O.I. Body weight as an indicator of the organism’s general condition while receiving iodine of organic and inorganic chemical origin under conditions of the optimal iodine supplementing. *Bulletin of problems in biology and medicine*. 2018. Iss. 1. No 1(142). P. 97–102. URL: https://doi.org/10.29254/2077-4214-2018-1-1-142-97-102.

18. Ryabukha O.I., Fedorenko V.I. Environmental determinants of thyroid pathology. *Medicni perspectivi*. 2021. Vol. 26. No. 3. P. 169–178. URL: https://doi.org/10.26641/2307-0404.2021.3.242253.

19. Meeus W., van de Schoot R., Keijsers L. et al. On the progression and stability of adolescent identity formation. A five-wave longitudinal study in early-to-middle and middle-to-late adolescence. *Child Development*. 2010. Vol. 81. No. 5. P. 1565–1581. URL: https://doi.org/10.1111/j.1467-8624.2010.01492.x.

20. Rietbergen C., Klugkist I., Janssen K.J. et al. Incorporation of historical data in the analysis of randomized therapeutic trials. *Contemporary Clinical Trials*. 2011. Vol. 32. No. 6. P. 848–855. URL: https://doi.org/10.1016/j.cct.2011.06.002.

21. van de Schoot R., Kaplan D., Denissen J. et al. A gentle introduction to bayesian analysis: applications to developmental research. *Child Development*. 2014. Vol. 85. No. 3. P. 842–860. URL: https://doi.org/10.1111/cdev.12169
22. Aguilera P.A., Fernandez A., Fernandez R. et al. Bayesian networks in environmental modelling. *Environmental Modelling & Software*. 2011. Vol. 26. No. 12. P. 1376–1388. URL: http://dx.doi.org/10.1016/j.envsoft.2011.06.004.

23. Tighe M., Pollino C.A., Wilson S.C. Bayesian networks as a screening tool for exposure assessment. *Journal of Environmental Management*. 2013. Vol. 123. P. 68–76. URL: http://dx.doi.org/10.1016/j.jenvman.2013.03.018.

24. van Someren E.P., Vaes B.L., Steegenga W.T. et al. Least absolute regression network analysis of the murine osteoblast differentiation network. *Bioinformatics*. 2006. Vol. 22. No. 4. P. 477–484. URL: http://dx.doi.org/10.1093/bioinformatics/bti816.

25. Lu K. On logistic regression analysis of dichotomized responses. *Pharmaceutical Statistics*. 2016. Vol. 16. No. 1. P. 55–63. URL: http://dx.doi.org/10.1002/pst.1777.

26. Whitley E., Ball J. 2002. Statistics review 1: Presenting and summarising data. *Critical Care*. 2016. Vol. 6. No. 1. P. 66–71. URL: https://doi.org/10.1186/cc1455.

27. Bewick V., Cheek L., Ball, J. Statistics review 7: Correlation and regression. *Critical Care*. 2003. Vol. 7. No. 6. P. 451–459. URL: https://doi.org/10.1186/cc2401.

28. Courvoisier D. S., Combescure C., Agoritsas T. et al. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *Journal of Clinical Epidemiology*. 2011. Vol. 64. No. 9. P. 993–1000. URL: https://doi.org/10.1016/j.jclinepi.2010.11.012.

29. Akoglu H. User’s guide to correlation coefficients. *Turkish Journal of Emergency Medicine*. 2018. Vol. 18. No. 3. P. 91–93. URL: http://dx.doi.org/10.1016/j.tjem.2018.08.001.

30. Schober P., Boer C., Schwarte L.A. Correlation Coefficients: Appropriate Use and Interpretation. *Anesthesia & Analgesia*. 2018. Vol. 126. No. 5. P. 1763–1768. URL: http://dx.doi.org/10.1213/ANE.0000000000002864.

31. Uurtio V., Monteiro J. M., Kandola J. et al. A Tutorial on Canonical Correlation Methods. *ACM Computing Surveys*. 2018. Vol. 50. No. 6. Article 95. URL: https://doi.org/10.1145/3136624.
32. Yadav S. Correlation analysis in biological studies. *Journal of the Practice of cardiovascular sciences*. 2018. Vol. 4. No. 2. P. 116–121. URL: http://dx.doi.org/10.4103/jpcs.jpcs_31_18.

33. Miot H. A. Correlation analysis in clinical and experimental studies. *Jornal Vascular Brasileiro*. 2018. Vol. 17. No. 4. P. 275–279. URL: http://dx.doi.org/10.1590/1677-5449.174118.

34. Rossi F.H., Volpato M.G., Metzger P.B. et al. Relationships between severity of signs and symptoms and quality of life in patients with chronic venous disease. *Jornal Vascular Brasileiro*. 2015. Vol. 14. No. 1. P. 22–28. URL: http://dx.doi.org/10.1590/1677-5449.20140039.

35. Maranzatto C.F., Miot H.A, Miot L.D. et al. Psychometrican analysis and dimensional structure of the Brazilian version of melasma quality of life scale (MELASQoL-BP). *Anais Brasileiros de Dermatologia*. 2016. Vol. 91. No. 4. P. 422–428. URL: http://dx.doi.org/10.1590/abd1806-4841.20165014.

36. Kim N., Fischer A.H., Dyring-Andersen B. et al. Research Techniques Made Simple: Choosing Appropriate Statistical Methods for Clinical Research. *Journal of Investigative Dermatology*. 2017. Vol. 137. No. 10. P. e173–e178. URL: http://dx.doi.org/10.1016/j.jid.2017.08.007.

37. Mutwil M., Usadel B., Schütte M. et al. Assembly of an interactive correlation network for the Arabidopsis genome using a novel heuristic clustering algorithm. *Plant Physiology*. 2010. Vol. 152. No. 1. P. 29–43. URL: https://doi.org/10.1104/pp.109.145318.

38. Batushansky A., Toubiana D., Fait A. Correlation-Based Network Generation, Visualization, and Analysis as a Powerful Tool in Biological Studies: A Case Study in Cancer Cell Metabolism. *BioMed Research International*. 2016. Article 2016(8313272). URL: http://dx.doi.org/10.1155/2016/8313272.

39. Kolmogorov A. N., Fomin S. V. Elementy teorii funktsiy i funktsionalnogo analiza [The Elements of the Theory of Functions and Functional Analysis]. Moscow: Nauka; 1976. 544 s.
40. Plashchevaya E.V., Smirnov V.A., Nigei N.V. et al. Osnovnyye vidy vrachebnuy logiki [The main types of medical logic]. In: Posobiye dlya prakticheskikh zanyatii po meditsinskoy informatike [Textbook for Practical Training in Medical Informatics]. Blagoveschensk: Amur State Medical Academy, 2014. p. 176.

41. Talbot P. Spacetime programming: a synchronous language for constraint search. In: Logic programming. Paris: Sorbonne University; Pierre and Marie Curie University; 2018. pp. 57–58. URL: https://hal.archives-ouvertes.fr/tel-01835496/document.

42. Bessmertnyy I.A., Nugumanova A.B., Platonov A.B. Osnovy logicheskogo programmirovaniya [Fundamentals of logical programming]. In: Intellektualnyye sistemy : uchebnik i praktikum dlya akademicheskogo bakalavriata [Intellectual Systems: a Textbook and Workshop for the Academic Bachelor]. Moscow: Yurayt; 2019. p. 31. URL: https://urait.ru/catalog/433716.

43. Rotshteyn A.P. Meditsinskaya diagnostika na nechetkoy logike [Medical Diagnostics under Fuzzy Logic]. Vinnitsa: Kontinent-Prim; 1996. 132 p.

44. Syavavko M., Rybytska O. Matematychne modeliuvannia za umov nevyznachenosti [Mathematical Modeling in Conditions of Uncertainty]. Lviv: Ukrainski Tekhnolohii; 2000. 319 p.

45. Patel A., Gupta S.K., Rehman Q. et al. Application of Fuzzy Logic in biomedical informatics. Journal of Emerging Trends in Computing and Information Sciences. 2013. Vol. 4. No. 1. P. 57–62. URL: http://www.cisjournal.org/journalofcomputing/Archive_Jan_2013.aspx.

46. Zadeh L.A. The roles of fuzzy logic and soft computing in the conception, design and deployment of intelligent systems. BT Technology Journal. 1994. Vol. 14. No. 4. P. 32–36. URL: https://doi.org/10.1109/FUZZY.1997.616336.

47. Gupta M. M. Forty-five years of fuzzy sets and fuzzy logic – A tribute to Professor Lotfi A. Zadeh (the father of fuzzy logic). Scientia Iranica. 2011. Vol. 18. No. 3. P. 685–690. URL: https://doi.org/10.1016/j.scient.2011.04.023.
48. Gürsel G. Healthcare, uncertainty, and fuzzy logic. *Digital Medicine*. 2016. Vol. 2. No. 3. P. 101–112. URL: [https://doi.org/10.4103/2226-8561.194697](https://doi.org/10.4103/2226-8561.194697).

49. Ryabukha O., Dronyuk I. Applying regression analysis to study the interdependence of thyroid, adrenal glands, liver, and body weight in hypothyroidism and hyperthyroidism. *CEUR Workshop Proceedings-Series*. 2019. Vol. 2488. P. 155–164. URL: [http://ceur-ws.org/Vol-2488/paper13.PDF](http://ceur-ws.org/Vol-2488/paper13.PDF).

50. Ryabukha O.I. Ultrastructural features of the follicular thyrocytes’ synthetic activity while taking organic iodine under conditions of alimentary iodine deficiency. *Bulletin of Problems in Biology and Medicine*. 2017. Iss. 4. No. 2(140). P. 134–139. URL: [https://vpbm.com.ua/ua/vipusk-4-tom-2-(140),-2017/9557](https://vpbm.com.ua/ua/vipusk-4-tom-2-(140),-2017/9557).

51. Ryabukha O.I. Search for markers of changes of the synthetic activity of thyrocyte under the influence of iodine reception in iodine deficiency conditions. *World of Medicine and Biology*. 2018. No. 3. P. 179–185. URL: [https://doi.org/10.26724/2079-8334-2018-3-65-179-185](https://doi.org/10.26724/2079-8334-2018-3-65-179-185).

52. Ryabukha O., Dronyuk I. The portraits creating method by correlation analysis of hormone-producing cells data. *CEUR Workshop Proceedings-Series*. 2018. Vol. 2255. P. 135–145. URL: [http://ceur-ws.org/Vol-2255/paper13.pdf](http://ceur-ws.org/Vol-2255/paper13.pdf).

53. Ryabukha O. I, Dronyuk I. M. Application of correlation analysis in cytology: Opportunities to study specific activity of follicular thyrocytes. *Regulatory Mechanisms in Biosystems*. 2019. Vol. 10. No. 3. P. 345–351. URL: [https://dx.doi.org/10.15421/021953](https://dx.doi.org/10.15421/021953).

54. Ryabukha O., Greguš ml M. Correlation analysis as a thyroid gland, adrenal glands, and liver relationship tool for correcting hypothyroidism with organic and inorganic iodine. *Procedia Computer Science*. 2019. Vol. 160. P. 598-603. URL: [https://doi.org/10.1016/j.procs.2019.11.041](https://doi.org/10.1016/j.procs.2019.11.041).

55. Ryabukha O.I. Application of mathematical approaches in medicine on the example of follicular thyrocytes secretory activity study. *World of Medicine and Biology*. 2019. No. 1. P. 181–187. URL: [https://doi.org/10.26724/2079-8334-2019-1-67-181](https://doi.org/10.26724/2079-8334-2019-1-67-181).
56. Ryabukha O., Dronyuk I. Applying of information technologies for study of the thyroid gland follicular thyrocytes' synthetic activity. CEUR Workshop Proceedings-Series. 2020. Vol. 2753. P. 323–337. URL: http://ceur-ws.org/Vol-2753/paper23.pdf.

57. Ryabukha O., Dronyuk I. Modern approaches to the applying of mathematical methods in the analysis of the transport direction of follicular thyrocytes. CEUR Workshop Proceedings-Series. 2021. Vol. 3038. P. 302–316. URL: http://ceur-ws.org/Vol-3038/paper19.pdf.

58. Ryabukha O.I. Study of ultrastructure profile of follicular thyrocytes’ transport capabilities by means of correlation analysis. Medical Informatics and Engineering. 2022. No. 3-4. P. 28–38. URL: https://doi.org/10.11603/mie.1996-1960.2021.3-4.12638.