Applying of Information Technologies for Study of the Thyroid Gland Follicular Thyrocytes' Synthetic Activity

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Abstract

Mathematical methods, which are traditionally used in biomedical diagnostics, operate on quantitative data, which makes it impossible to use them in the study and interpretation of qualitative cytophysiological data. Descriptive (linguistic) approaches that use the principles of fuzzy logic are becoming more and more widespread in the study of qualitative biomedical information. The combination of modern information technology and cytophysiological concepts permits a holistic cybernetic understanding of cell activity as a supersystem with complex links between its subsystems. In the presented work, the complex use in the thyroid follicular thyrocytes study of such mathematical approaches as correlation analysis, the principle of phase interval, mathematical statistics, quantitative analysis of electron microscopy images and the method of determining profiles of hormone-producing cells' special capabilities, which permits to transform qualitative (linguistic) characteristics of thyroid gland thyrocytes' organelles into quantitative parameters with their further transformation and the obtained results objectification by means of correlation portraits. The data obtained in this way were used to analyze the dependences of some constituent elements of the cell (cell organelles) on other ones in studying the influence of the same factor on the peculiarities of cell activity changes in different experimental conditions.

Keywords 1

mathematical methods in cytology, biomedical research, thyroid gland, iodine deficiency, inorganic iodine, thyrocyte, synthesis of thyroid hormones

1. Introduction

Holistic view of the cell as a supersystem with complex relationships between its components should be formed using mathematical methods, which can be used to determine the main features of its functioning. Today, advances in information theory and cybernetics permit to apply mathematical technologies in almost all spheres of life: data obtained through mathematical analysis can be used to formulate hypotheses about the dependence of some phenomena on others [1,2]. They can be especially important in the study of normal cell activity and pathology [3]. At the same time, physiological and pathological processes have a number of interrelated features of qualitative and quantitative nature, which ultimately are the most appropriate in terms of its structure and appropriate for realization of potential opportunities. The main features of the cell as a biological system are: a certain property of its constituent elements, their manifestations intensity, the type of connections between the elements, the density of connections between the components of the system. Each element of such a system can be in different states - normal vital activity, excitation, functional stress, emergency regulation, functional or organic changes, according to which their characteristic

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morphofunctional features are formed. If the properties of each element in the system are described using certain parameters and variables, their transformations can be displayed in the form of functional dependencies [4].

An original approach to the involvement of mathematical technologies in the process of studying the activity of hormone-producing cells was first published [5] and proposed as a method of studying changes in their functional activity under the influence of various factors [6]. This permits using mathematical technologies to reveal the patterns of physiological and pathological processes, to clarify their patterns and to predict the consequences of various processes.

Modern biomedical diagnostics as a fundamental element of medical science is increasingly using the possibilities of mathematical analysis. Any task of biomedical diagnostics can be considered as search for data display:

$$X^* = (x_1^*, x_2^*, \ldots x_n^*) \rightarrow d_j \in D = (d_1, d_2, \ldots d_m), \quad (1)$$

where X^* is the set of parameters of a particular patient's condition/organ/cell/organelle and D is the set of diagnoses.

To solve the problems of biomedical diagnostics, the most widespread are mathematical methods, such as Bayesian analysis [7], regression analysis [8], the logical programming [9]. Summarizing the possibilities of their use, it should be noted that they are poorly adapted to work with quality (non-numerical) databases [10]. However, in biomedical practice, the analysis of qualitative information, which is given in linguistic form and is mostly heuristic, is very important for correct diagnosis.

To solve various biomedical problems that require mathematical processing of non-numerical (linguistic) information, fuzzy set theory is increasingly used [11]. For the successful implementation of biomedical diagnostics using fuzzy logic it is necessary to adhere to the principle of linguistic diagnosis, parameters of the patient's condition and the principle of linguistic diagnostic data [12]. Unlike traditional models, which are built on the principles of quantitative mathematics, the adequacy of fuzzy logical statements does not change with slight fluctuations in the experimental conditions. At the same time, practical application of fuzzy set theory for the study of biological objects or diagnosis is quite cumbersome, and a clear gradation of the biological system's states is not always possible. An important reason is the lack of a sufficient number of specially trained experts.

The use of electron microscopy permits to study in detail the basic level of the living matter's hierarchical organization - cellular organelles in the norm and in the restructuring of their substructural components in the conditions of impaired functional balance and pathology. The study of cell ultraarchitectonics is carried out in several ways. The most commonly used is descriptive method, which involves the use of words in the language used. The linguistic approach to the analysis of the electron microscopic picture of the studied tissue has undeniable advantages. They include a detailed *status quo* statement, reflection of the studied ultrastructures state nuances, the capability to draw conclusions about the system's functional state. At the same time, this approach is purely empirical and has significant shortcomings, such as subjectivity in description, the need for highly qualified specialists to carry out studies, the inability to use the results for further mathematical transformations in the need to analyze the process course or to predict its consequences. The use of computer software, which can be used to determine the area or percentage of certain structural components in the cell cytoplasm, enriches the research potential in the study of ultrathin cell structure.

However, display of the cell state by means of unrelated numbers does not solve the problem of a comprehensive study of its activity, as it does not always permit to correctly determine the degree of structural changes, their direction and functional significance. Given the shortcomings of the descriptive (linguistic) approach to the study of electron microscopy images and determination of the percentage of individual organelles in the cell, it seems possible to apply the principle of fuzzy logic. An example of using this approach to the study of the thyroid gland's follicular thyrocytes can be a description of their morphofunctional state with reduced functional activity:

"*If* the shape of the cell is prismatic; electron density of cytoplasm - insignificant; electron density of colloid - is insignificant; apical microvilli - very thick, very thin, long; the number of apical microvilli - is significant; mitochondria in small quantities; the value of the rough endoplasmic reticulum elements - is significant; the magnitude of the Golgi apparatus elements - is significant; the number of free ribosomes and polysomes - is insignificant; the number of lysosomes - is insignificant; the number of apical secretory granules - is insignificant, *then* the functional activity of the thyrocyte is reduced (pathological)."

A significant advantage of this approach to the study of electron microscopy images is the capability of mathematical transformations with subsequent conclusions and generalizations. At the same time, it is not adapted to determine all the nuances of the morphofunctional state, in which the cell is.

Thus, medical diagnostics is a decision-making process in a cybernetic system with *n* input parameters (cause/signs of the condition) and a single output parameter, which is the consequence/ conclusion/diagnosis. Although the need to develop modern diagnostic decision-making systems in various fields of medicine is extremely urgent, the tools for creating such systems for cytology need significant improvement. This is primarily due to the insufficient efficiency of those mathematical methods that are traditionally used to model the relationships between condition parameters and diagnosis. In addition, they are not adapted to study the functional activity of the cell, which significantly limits the development of scientific knowledge in the field of cytology.

2. Purpose of the study

Based on the analytical generalization of scientific literature, to determine the capability of using common mathematical methods for studying the ultrathin structure of hormone-producing cells and, based on the results of our own observations, to choose the most informative method to determine the characteristics of changes in hormonal cells ultrastructures under the effect of medicinal products, that permits to make substantiated conclusions both on the reliability of cytophysiological study and the efficacy of the applied means for correcting endocrine disorders.

3. Materials and methods of the study

The main research methods were:

- Analytical review, synthesis and generalization of data obtained from scientific literature sources on the research topic.
- Mathematical statistics [13]. Numerical data for assessing the number and condition of cellular ultrastructures are used to determine $\bar{x}$ - the arithmetic mean and *m* - the standard deviation of the arithmetic mean, which is calculated by commonly used formulas.
- The principle of phase interval [14,15]. The condition or number of studied cellular ultrastructures is compared to two diametrically opposed controls - the norm and the studied untreated pathology.
- Elements of correlation analysis [16]. The cell is considered to be a complex negentropic system, the subsystem of which is a certain studied field of its activity. To establish the relationships between its constituent elements and to study their strength and direction, the pairwise correlation coefficients are determined, which are calculated according to Pearson's formula (2):

$$r_{xy} = \frac{\sum_{i=1}^{i=n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{i=n}(x_i - \bar{x})^2 \sum_{i=1}^{i=n}(y_i - \bar{y})^2}}, \quad (2)$$

where r_{xy} - coefficient of pair correlation between the indices *x* and *y*; x_i - the *x* index value in *i* - observation; y_i - the y index value in *i*-observation; *n* - number of observations, $\bar{x}$ - mean value of the *x* index for *n* observations performed; $\bar{y}$ - mean value of the *y* index for *n* observations performed [4].

A positive value of the pairwise correlation coefficient r_{xy} indicates the same direction of the studied index'es changes, negative value means that with the increase in one of the indices another index associated with it decreases; the r_{xy} value = 1.0 indicates the existence of a direct proportionality between the indics x and y, $r_{xy} = -1.0$ mean inverse proportionality. In the structural organization of relationships between the indices, the most significant are considered to be very strong and strong correlations, which on the Chaddock scale of linear correlation [17] are within the range of $1.0 \geq r_{xy} \geq 0.91$ and $0.9 \geq r_{xy} \geq 0.71$, respectively; in the absence of such correlations, significant correlations $0.7 \geq r_{xy} \geq 0.51$ are taken into consideration.

- Fundamental principles of fuzzy set theory are: the principle of linguistic diagnosis and the patient's condition parameters, and the principle of linguistic diagnostic data [18].
- Semi-quantitative analysis of electron microscope images [6]. The analysis of electron microscope images of follicular thyrocytes' ultrastructures is performed according to a certain algorithm. Numerical assessment of the symptoms manifestation degree of ultrastructural elements is carried out using graphic symbols or a point/percentage scale. Absence of a sign is assessed as 0 points, insignificant manifestations - 1 point, moderate manifestations - 2 points, significant manifestations - 3 points, the maximum manifestations of a sign - 4 points. The increase in the number of ribosomes is proposed to be assessed in proportion to the degree of its severity within the range from 4 to 8 points. The scale for assessing the signs manifestations in the semi-quantitative analysis of electron microscope images is given in Tab. 1.

Table 1
Scale for assessing the symptoms manifestations

Symptom manifestation degree	Graphic symbol	Numerical assessment	
		(points)	(percentage)
feature absent	-	0	0
weak	+	1	25
moderate	++	2	50
significant	+++	3	75
maximal	++++	4	100

Note. 0 points - state of unattended pathology under study ("disease"); 4 points - state of the studied pathology complete absence ("health")

- Method for determining the profiles of hormone-producing cells' special capabilities [6]. If any field of a hormone-producing cells's activity is qualified as "opportunity" and cellular ultrastructures which implement it are defined, the consequence of such quantification will be creation of narrow specialized clusters - profiles of the respective opportunities. For the mathematical analysis of the obtained data, each quality of each ultrastructural element is attributed the appropriate symbol with the subsequent digital assessment of the signs' manifestations degree. In our work, we present the ultrastructural components to the profile of the thyroid gland follicular thyrocytes' synthetic capability (Tab. 2).

Table 2
Ultrastructural components to the profile of the thyroid gland follicular thyrocytes' synthetic activity

Ultrastructural element	Studied feature of the ultrastructural element	Status of the studied ultrastructural element feature	Symbol legend of the studied ultrastructural element feature
Cytoplasm	electron density	insignificant	B1
		moderate	B2
		significant	B3

Rough endoplasmic reticulum (rough ER)	structure	constricted	J1
		normal	J2
		increased	J3
	number of membrane bound ribosomes	reduced	J4
		moderate	J5
		increased	J6
Free ribosomes (in cytoplasm) and polysomes	number	reduced	K1
		moderate	K2
		increased	K3
Golgi apparatus	structure	constricted	L1
		normal	L2
		expanded	L3

The study was carried out on 20 white nonlinear male rats with the initial body weight of 140–160 g, which under standard vivarium conditions consumed an isocaloric semi-synthetic starch-casein iodine deficient diet. Group 1 rats were kept under the conditions of unpotentiated alimentary iodine deficiency; in rats of group 2 alimentary iodine deficiency was potentiated by administering the thyrostatic drug mercazolyl (Mercazolyl-Health, RF) at the dose of 3 mg/kg body weight. Correction of iodine deficiency in animals of both groups was carried out with inorganic iodine at the dose of 100 μg/kg body weight. The duration of the experiment was 30 days; during observation and euthanasia, the principles of bioethics were observed in compliance with the European Convention for the Protection of Vertebrate Animals Used in Experiments (Strasbourg, 1986) and Council of Europe Directive 2018/63/ CV.

The subject to study were electron microscope images of ultrathin (4–6 μm) thyroid glands sections in rats of both groups made according to generally accepted methods. Processing of the obtained results was performed by the scale for assessment of thyrocyte ultrastructural elements' manifestations using the semi-quantitative analysis of electron microscope images (Tab. 1) by means of software: for digital data - StatSoft Statistica v6.0 package, for correlation tables and portraits - Microsoft Office 2010 package - electronic MS Excel spreadsheet and MS Word graphic editor (Microsoft Graph), respectively.

4. Results and discussion

In order to avoid the shortcomings inherent in the considered methods of cell research, we proposed a method of constructing correlation portraits in different fields of hormone-producing cells' activity [6]. Interpretation of the obtained data is carried out from the standpoint of cytophysiology, taking into account the functional significance and role of each cellular ultrastructure [19,20].

As an example of our method's informativeness in the study of functionally related conditions, we present correlation portraits with their description and cytophysiological interpretation of the interdependencies established between cellular organelles that synthesize hormones in follicular thyrocytes of the thyroid glands. In the given case, the synthesis is carried out under the conditions of varying severity hypothyroidism:

1. caused by alimentary deficiency of iodine (less severe).
2. caused by alimentary iodine deficiency, potentiated by consuming the thyrostatic drug mercazolyl (more severe).

4.1. Database of significant data for constructing correlation portraits

The presence of correlation connections between ultrastructural elements of the synthetic activity of the thyroid glands follicular thyrocytes in rats, their strength and direction are presented in Tab. 3, and Tab. 4.

Table 3

Correlations between the constituent elements of the synthetic direction portrait of thyroid glands follicular thyrocytes' activity in white male rats who were corrected alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

Interdependent ultrastructural elements of the portrait		Correlation, (r)
Characteristics of the studied ultrastructural elements	Ultrastructural elements features legends	
moderate number of bound ribosomes - moderate number of free ribosomes	J5 – K2	1.000
normal structure of rough ER - moderate number of bound ribosomes	J2 – J5	0.612
normal structure of rough ER - moderate number of free ribosomes	J2 – K2	0.612
increased structure of rough ER - expanded structure of Goldgi apparatus	J3 – L3	0.612
increased structure of rough ER - normal structure of Goldgi apparatus	J3 – L2	0.612
moderate number of bound ribosomes - normal structure of Goldgi apparatus	J5 – L2	0.667
moderate electron density of cytoplasm - increased structure of rough ER	B2 – J3	–0.612
moderate number of free ribosomes - normal structure of Goldgi apparatus	K2 – L2	–0.667
expanded structure of Goldgi apparatus - normal structure of rough ER	L3 – J2	–0.612

Table 4

Correlations between the constituent elements of the synthetic direction portrait of thyroid glands follicular thyrocytes' activity in white male rats who were corrected mercazolyl-potentiated alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

Interdependent ultrastructural elements of the portrait		Correlation, (r)
Characteristics of the studied ultrastructural elements	Ultrastructural elements features legends	
reduced number of free ribosomes - normal structure of Goldgi apparatus	K1 - L2	1.000
normal structure of rough ER - moderate number of bound ribosomes	J2 - J5	0.764
reduced number of bound ribosomes - moderate number of free ribosomes	J4 - K2	0.873
moderate number of free ribosomes - expanded structure of Goldgi apparatus	K2 - L3	0.764
insignificant electron density of cytoplasm - moderate number of free ribosomes	B1 - K2	–0.801
moderate electron density of cytoplasm - increased structure of rough ER	B2 - J3	–0.764
increased structure of rough ER - reduced number of free ribosomes	J3 - K1	–0.873
increased structure of rough ER - normal structure of Goldgi apparatus	J3 - L2	–0.873

moderate number of bound ribosomes - moderate number of free ribosomes	J5 - K2	–0.764
insignificant electron density of cytoplasm - moderate number of bound ribosomes	B1 - J5	0.612
moderate electron density of cytoplasm - moderate number of bound ribosomes	B2 - J5	0.667
moderate electron density of cytoplasm - reduced number of free ribosomes	B2 - K1	0.667
reduced number of bound ribosomes - expanded structure of Goldgi apparatus	J4 - L3	0.667
reduced number of free ribosomes - expanded structure of Goldgi apparatus	K1 - L3	0.667
normal structure of Goldgi apparatus - expanded structure of Goldgi apparatus	L2 - L3	0.667
expanded structure of Goldgi apparatus - insignificant electron density of cytoplasm	L3 - B1	–0.667
moderate number of bound ribosomes - increased number of bound ribosomes	J5 - J6	–0.667

4.2. Correlation portraits of follicular thyrocytes' synthetic capability, description and interpretation of traced correlations

When consuming 100 μg of inorganic iodine under the conditions of alimentary hypothyroidism due to iodine deficiency, we established only 1 very strong correlation ($1.0 \geq | r | \geq 0.91$) and did not trace strong ($0.9 \geq | r | \geq 0.71$) correlations, therefore the study was carried out using significant ($0.7 \geq | r | \geq 0.51$) correlations, which there were 8; 5 of them being indirect (Fig. 1).

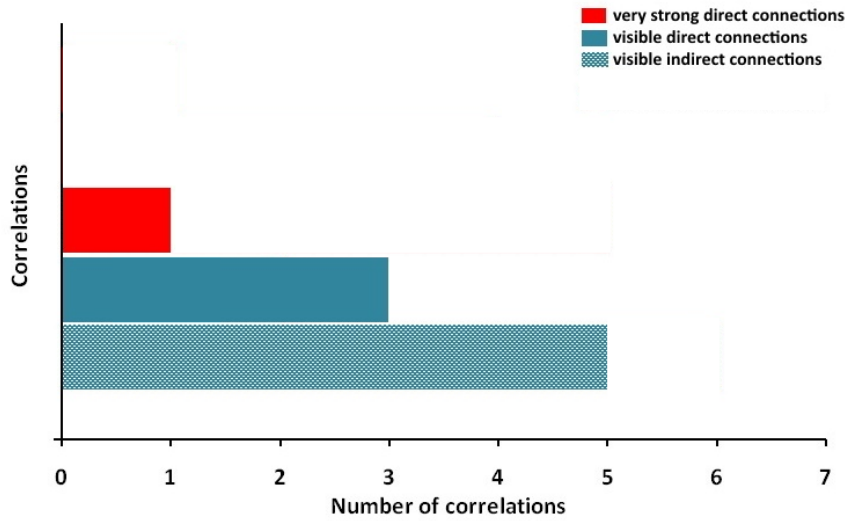

Figure 1: Ranking by the number and strength of significant correlations traced between protein-synthesizing ultrastructures of thyroid follicular thyrocytes in male white rats who were corrected alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

The actual signs of the synthetic capability profile's correlation portrait when consuming 100 μg of inorganic iodine under the conditions of alimentary hypothyroidism due to iodine deficiency were B2, J2, J3, J5, K2, L2, L3 (Fig. 2). The focal points of the portrait were J2, J3, J5, K2, L2, which formed 3 relationships, and L3 (2 relationships). The structure of the portrait was unstable: due to the

predominance of indirect correlations (5 out of 9 significant ones in total), it had a great tendency to change.

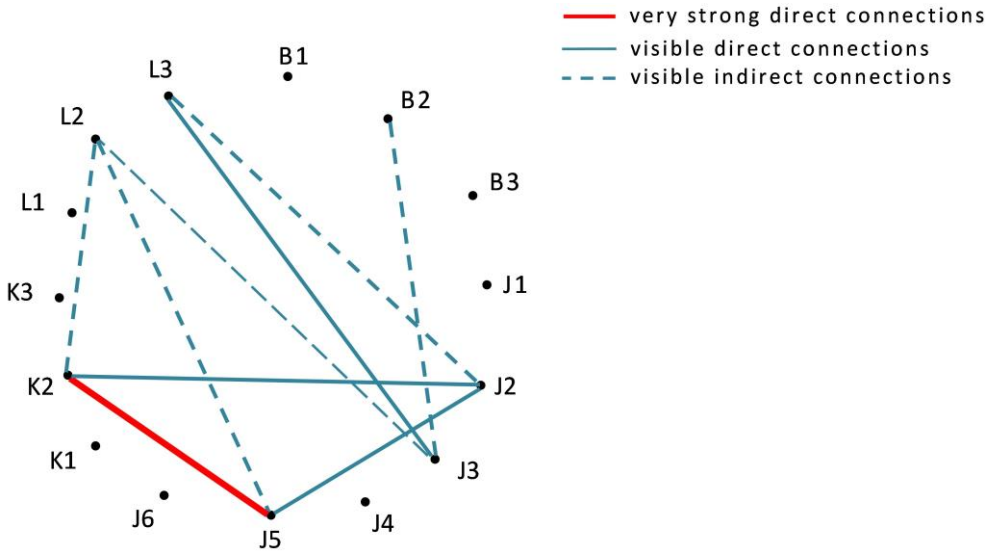

Figure 2: Graphic representation of the correlation portrait profile structure of the thyroid glands follicular thyrocytes' synthetic activity of white male rats who were corrected alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

It was found that under the studied conditions the Goldgi apparatus was of paramount importance for thyroid hormonal poetics. Thus, the synthesis of hormones occurred by the coordinated interaction of Goldgi apparatus and rough ER ultrastructures, which were in the same functional state: the expanded elements of Goldgi apparatus (L3) interacted (r = 0.612) with the expanded ultrastructures of rough ER (J3). Indirectly, this is confirmed by indirect correlations of the same force (r = –0.612) traced between the extended elements of the Goldgi apparatus (L3) and moderately expressed (normal structure) elements of rough ER (J2) and between Goldgi apparatus substructures of moderate (normal) size (L2) and extended elements of rough ER (J3).

A very strong relationship between moderate amounts of ribosomes on rough ER membranes (J5 - bound ribosomes) and in the cytoplasm of thyrocytes (K2- free ribosomes) indicates the correlation between ribosomes of different localization and may indicate the prerequisites for the normal course of the synthetic process in the cell. At the same time, the synthetic activity of thyrocytes occurred against the background of a certain functional stress. This is evidenced by the indirect correlations of the Goldgi apparatus elements, which were moderate in size (L2) with a moderate number of ribosomes on rough ER membranes (J5) and a moderate number of ribosomes in the cytoplasm (K2).

Thus, in the conditions of alimentary hypothyroidism caused by iodine deficiency, consuming a large (100 μg) dose of inorganic iodine has a moderately beneficial effect on the interaction between the organelles that implement the synthesis of the hormonal product. In particular, the increasing role of the Goldgi apparatus, in which the maturation of hormone molecules takes place, has been established, which can be logically interpreted as a sign of the hormonopoiesis completion. However, the presence of certain dissociations between the morphofunctional states of protein-synthesizing organelles indicates the preservation of functional stress due to iodine deficiency, which does not decrease when consuming 100 μg of inorganic iodine.

The actual signs of the ultrastructural elements state in the correlation portrait of the thyrocytes synthetic capability profile when consuming 100 μg of inorganic iodine under mercazolyl-potentiated alimentary hypothyroidism due to iodine deficiency were B1, B2, J2, J5, K4, L2, L3, between which the following correlations are traced: very strong (1,0 ≥ | r | ≥ 0,91) - 1, strong (0,9 ≥ | r | ≥ 0,71) - 8 (from them 5 being indirect). For the objective characterization of the portrait, noticeable (0.7 ≥ | r | ≥ 0.51) correlations were studied, of which 8 were established - 2 of them being indirect (Fig. 3).

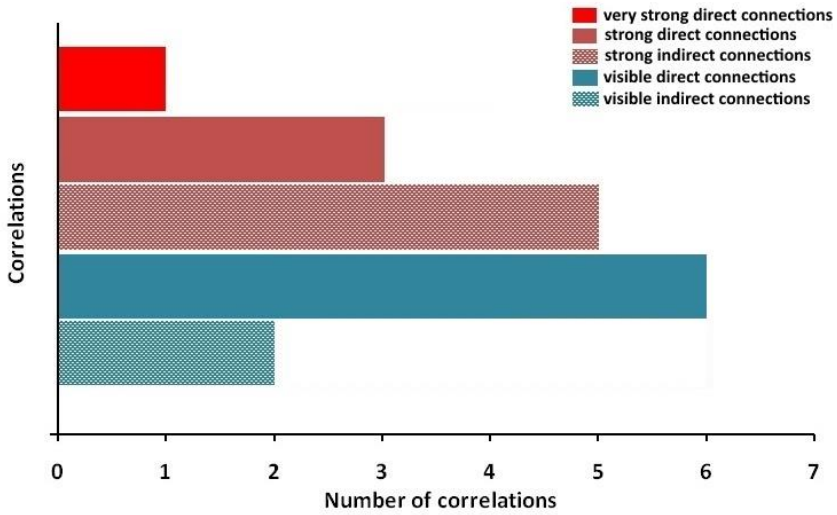

Figure 3: Ranking by the number and strength of significant correlations traced between protein-synthesizing ultrastructures of thyroid follicular thyrocytes in male white rats who were corrected mercazolyl-potentiated alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

The main focal points of the portrait were J5, L3 (5 corelations in total) and B2, K2, L2 (which had 4 significant correlations); focal points J3 and B1 formed 3 significant correlations. The architectonics of the portrait was characterized by symmetry, its structure – by stability and low ability to change (Fig. 4).

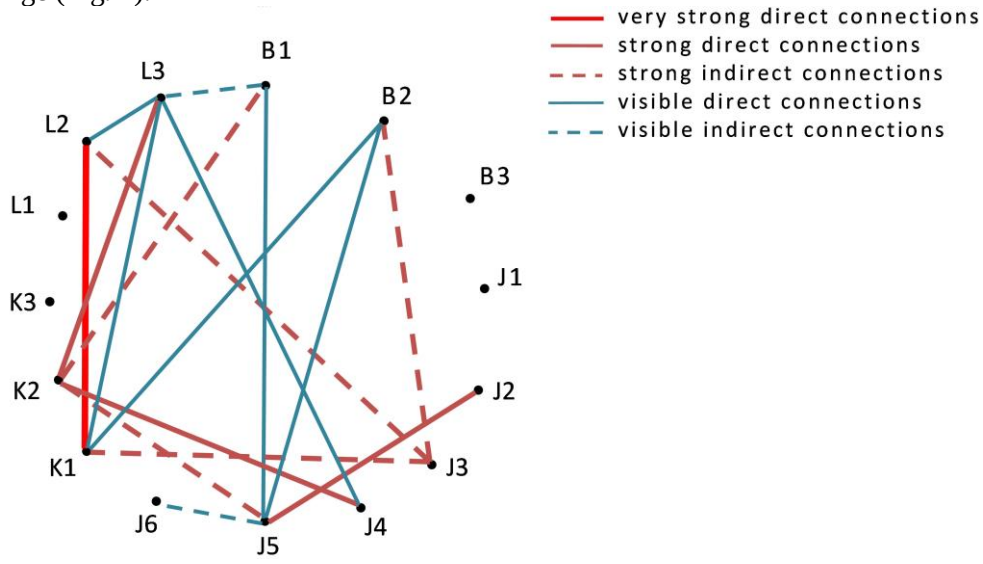

Figure 4: Graphic representation of the correlation portrait profile's structure of the thyroid glands follicular thyrocytes' synthetic activity in white male rats who were corrected mercazolyl-potentiated alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

The strong relationship between moderate (normal structure) rough ER substructures (J2) and moderate number of ribosomes on its membranes (J5) indicates sufficient synthetic thyrocyte activity. Indirectly, this is confirmed by indirect correlations of the same strength which rough ER with extended substructures (J3) formed with moderately pronounced (normal structure) elements of the Goldgi apparatus (L2), reduced number of free ribosomes and polysomes (K1) and moderate electron density of cytoplasm (B2).

Consuming a large dose (100 μg) of inorganic iodine caused a functional stress of the thyrocyte, as evidenced by the involvement of a significant number of ultrastructures in the synthetic process. In particular, we observed four complexes of correlations with different composition and strength: a very strong correlation of the Goldgi apparatus with moderately expressed (normal) substructures (L2) and

a small number of (free) ribosomes in the cytoplasm (K1); strong correlation of a small number of bound ribosomes (J4) and a sufficient (normal) number of free ribosomes (K2); a direct strong correlation of a sufficient number of free ribosomes (K2) and a Goldgi apparatus with extended elements (L3) and an indirect correlation of a sufficient number of free ribosomes (K2) and a small electron density of the cytoplasm (B1); a noticeable correlation between the Goldgi apparatus with extended elements (L3) and a small number of free ribosomes (K1). In addition, the strong correlation of a sufficient number of free ribosomes (K2) with the extended elements of the Goldgi apparatus (L3) and the strong indirect correlation of K2 with a low electron density of the cytoplasm (B1) may indicate that the number of free ribosomes is not is crucial for the protein-synthesizing function of the Goldgi apparatus.

Therefore the large number of dissociations between morphofunctional states of such important for synthetic thyrocyte activity ultrastructures as Goldgi apparatus and (free) cytoplasmic and (bound) membrane-fixed rough ER ribosomes, indicates that when potentiating alimentary hypothyroidism with mercazolyl in the conditions of iodine deficiency consuming a large dose (100 μg) of iodine not only leads to significant functional stress of the thyrocyte, but can also significantly impede the thyroid hormones synthesis.

Thus, the practical application of our method has shown its great informative value in cytomorphological studies. With its help it is established that in the conditions of impaired functional balance caused by both alimentary deficiency of iodine, and the combined influence of alimentary iodine deficiency and the thyrostatic drug mercazolyl, preconditions for realization of the thyrocyte's synthetic activity remain. At the same time, correction of iodine deficiency by administering a large dose (100 μg) of inorganic iodine excessively activates its activity, which increases functional stress, and potentiation of alimentary iodine deficiency with mercazolyl may lead to impaired thyrocyte adaptation to these adverse factors.

We also found the features of ribosomes participation in the synthesis of thyroid hormones in different functional states of the thyroid gland. The correlations established between ribosomes and other protein-synthesizing organelles permitted to determine the peculiarities of the synthetic process in terms of unpotentiated and potentiated iodine deficiency (Tab. 5). In the presented Fig. 5, and Fig. 6, the differences in the correlations of ribosomes with other protein-synthesizing ultrastructures under the studied conditions are well observed. For better perception of information, the organelles that are the closest to the norm in their characteristics are marked with green color. Organelles that are far from the norm in opposite directions are marked: when the characteristics decrease - violet-colored, when they increase - marked with orange.

Under the conditions of consuming a large dose (100 μg) of inorganic iodine in unpotentiated alimentary iodine deficiency (Fig. 5) the correlation between sufficient numbers of ribosomes fixed on the rough ER (J5 - bound ribosomes) membranes, and ribosomes located in the thyrocyte cytoplasm (K2 - free ribosomes) indicate the equal value of both free and fixed ribosomes for the hormonal synthesis processes.

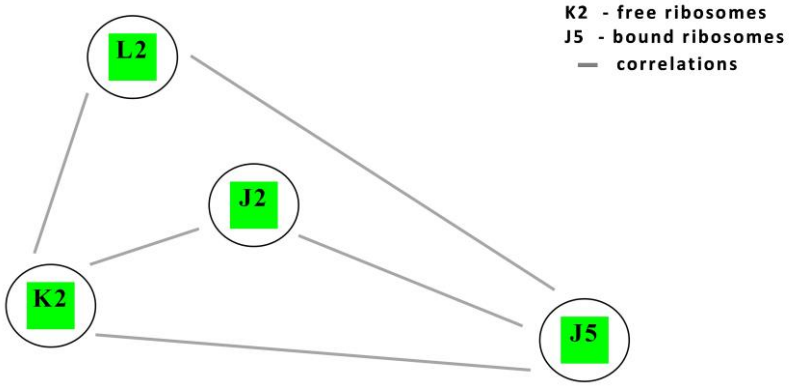

Figure 5: Scheme of significant direct correlations traced between ribosomes and other profile components of the thyroid follicular thyrocytes' synthetic activity in white male rats who were corrected alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

Instead, in the conditions of mercazolyl-potentiated alimentary iodine deficiency, consuming a large dose (100 μg) of inorganic iodine leads to impaired hormonopoiesis. This is evidenced by the numerous correlations of reduced (K1) or moderate (K2) number of free ribosomes with other ultrastructures, which functional states are not adequate for the number of ribosomes (Fig. 6). Strong correlations of free ribosomes moderate number (K2) with reduced number of bound ribosomes J4 (r = 0.873) and moderate number of bound ribosomes J5 (r = –0.764) indicate differences in the functional purpose of ribosomes with different intrathyrocyte localization. This promotes a more detailed study of ribosomes involvement in the synthesis of thyroid hormones: the number, location and correlations of ribosomes with other protein-synthesizing ultrastructures are determined by the functional status of the thyrocyte and change accordingly. In this case, a detailed description of the thyrocyte ribosomes' status can serve as a marker of the appropriate morphofunctional changes.

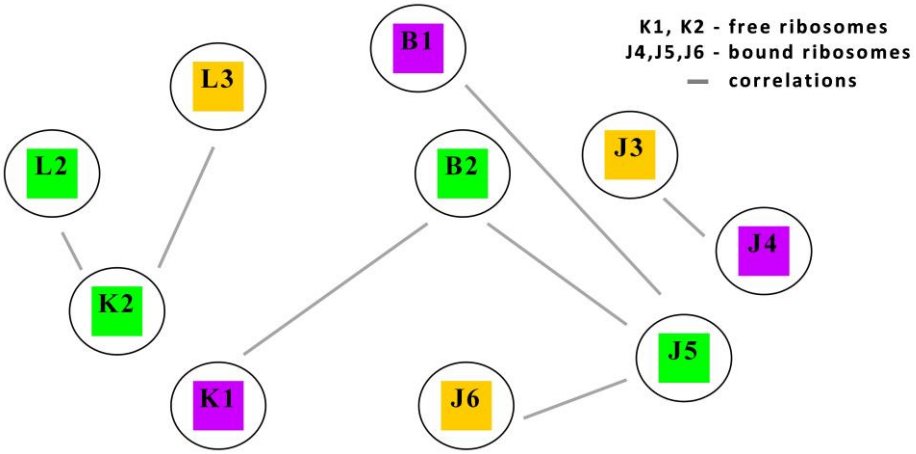

Figure 6: Scheme of significant direct correlations traced between ribosomes and other components of the synthetic activity profile of white male rats' thyroid follicular thyrocytes who were corrected mercazolyl-potentiated alimentary iodine deficiency with a large dose (100 μg) of inorganic iodine

Table 5

Changes in thyroid follicular thyrocytes' protein-synthesizing activity according to the results of ribosomes interrelations analysis with different localization among themselves and with other protein-synthesizing substructures

Experimental conditions	Type and number of ribosomes		Protein-synthesizing cellular substructures	Significant correlations between ribosomes and protein-synthesizing cellular substructures	Importance of established correlations for synthetic activity
Iodine deficiency in the diet	bound	moderate	normal structure of rough ER	0.612	↑ (moderate increase)
		moderate	moderate number of free ribosomes	1.0	↑↑↑ (intense increase)
		moderate	normal structure of Golgi apparatus	–0.667	↘ (moderate impairment with functional stress)

	free	moderate	normal structure of rough ER	0.612	↑ (moderate increase)
		moderate	normal structure of Golgi apparatus	–0.667	↘ (moderate impairment with functional stress)
Potentiated iodine deficiency in the diet	bound	reduced	moderate number of free ribosomes	0.873	↑↑ (significant Increase)
		reduced	extended structure of Golgi apparatus	0.667	↑ (moderate increase)
		moderate	normal structure of rough ER	0.764	↑↑ (significant increase)
		moderate	insignificant electron density of cytoplasm	0.612	↑ (moderate increase)
		moderate	moderate electron density of cytoplasm	0.667	↑ (moderate increase)
		increased	moderate number of bound ribosomes	–0.667	↘ (moderate impairment with functional stress)
	free	reduced	extended structure of rough ER	–0.873	↘↘ (significant impairment with functional stress)
		reduced	moderate electron density of cytoplasm	0.667	↓ (moderate impairment)
		reduced	normal structure of Golgi apparatus	1.0	↘↘↘ (intense impairment with functional disorder)
		reduced	extended structure of Golgi apparatus	0.667	↘ (moderate impairment with functional stress)
		moderate	reduced number of free ribosomes	0.873	↑↑ (significant increase)

	moderate	extended structure of Golgi apparatus	0.764	↗↗ (significant increase with functional stress)
	moderate	insignificant electron density of cytoplasm	–0.801	↘↘ (significant impairment with functional stress)
	moderate	moderate number of bound ribosomes	–0.764	↘↘ (significant impairment with functional stress)

Note. The number and direction of the "arrow" symbol indicates ranking of the intensity and direction of changes in the protein-synthesizing activity of follicular thyrocytes

5. Conclusions

1. Mathematical methods, traditionally used in medicine, operate mainly with quantitative data, and the method of fuzzy logic, which uses qualitative information, does not permit to take into account all the nuances of cellular ultrastructures' condition and requires a rather strict determinism, which is not always possible to achieve in cell studies. This actually makes it impossible to use these methods for the needs of cytophysiological studies.

2. The combination of mathematical and morphological methods proposed for studying the activity of hormone-producing cells can be attached to modern biomedical information technologies, as it is an independent research method, by which the features of cell morphophysiology are studied from the standpoint of its priority self-regulation. This permits to analyze the relationships between cellular ultrastructures (their presence, direction, strength) and deepens the understanding of cell function in different states and conditions, which greatly expands the possibilities of cytophysiology as a science.

3. The use of a package of such interrelated mathematical and morphological methods as fundamental elements of correlation analysis, the principle of phase interval and mathematical statistics, semi-quantitative analysis of electron microscope images and determination of profiles for special capabilities of hormone-producing cells permits to transform qualitative characteristics of cell organelles into quantitative parameters with the capability of further objectifying the results obtained. An important feature of the proposed research method is the lack of strict determinism, which is not inherent in biological objects.

4. The use of ideas about the cell as a complex self-regulatory system, in which the point of application of different factors having the same direction of influence are different organelles with the similar functional specialization, permits to identify and analyze the existing differences in cell activity according to their manifestations and force.

5. Construction of correlation portraits in certain fields of cell activity, their further analysis and generalization permit to study the relationships and interdependencies between ultrastructures in different functional states of the cell and contribute to the detailed characterization of ultrastructural changes influenced by different factors in different living conditions. In this case, the correlation portrait becomes a multi-component multivariate expert system.

6. The represented method of studying the hormone-producing cells by constructing correlation portraits of certain fields of its activity permits to characterize the nuances of its condition and to establish the functioning features not only at the time of study, but also permitting to study changes in intimate mechanisms of hormonopoiesis and to determine reserve and potential capabilities.

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