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The Capabilities of Artificial Intelligence to Simulate the Emergence and Development of Diseases, Optimize Prevention and Treatment Thereof, and Identify New Medical Knowledge

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Abstract

Objectives: To show and clearly demonstrate by examples that the possibilities of the artificial intelligence methods in the field of medicine are much wider than those currently used. Almost all the known studies in this field are reduced to diagnosing various kinds of diseases at a given time, or to predicting their outcomes in an indefinite future. Modern literature lacks information on dynamic mathematical models that treat diseases as time-evolving processes. In this regard, the mathematical modeling method is practically not used to solve the problem of choosing optimal strategies for the prevention and treatment of diseases, which is very important for medical practice.

Methods: Four methods of creating dynamic mathematical models based on neural networks were proposed and tested in this paper. The first of these methods implements the idea of adding neural network knowledge with the knowledge embedded in the SCORE scale. The second and third methods represent modifications to the sliding window method. The fourth method has no rigorous justification and refers to the heuristic techniques that reflect the authors' experience in the application of neural network technologies in various fields of knowledge.

Results and Conclusion: Based on the cardiovascular system diseases, it has been shown that our mathematical models allow us not only to diagnose diseases at the current moment, but also to predict their appearance and development in future periods of life, and also to select the optimal strategy for their prevention and treatment, taking into account the patient's individual parameters. The article shows the possibility of identifying new medical knowledge using mathematical models. The conclusion that recommendations for the prevention and treatment of cardiac patients should be given strictly individually, taking into account the physiological characteristics of the patient's body, has been made. While for some patients such recommendations as: "to limit the use of sweet", "to stop smoking", "to take drugs that reduce blood pressure," etc. are really useful, for other they can cause harm. The proposed diagnostic and prognostic system allows identifying such non-standard patients and avoiding erroneous recommendations. The demonstration prototype of the diagnostic and prognostic system is freely available in the "Projects" section at the website www.PermAi.ru.

Keywords: *diagnostics, neural network, prediction, prevention, simulation.*

INTRODUCTION

As is known, more than 700 years ago the Spanish scientist and theologian Raymond Lully was the first who attempted to apply methods of artificial intelligence in the field of medicine. He created the world's first expert system in the form of a mechanical device, which allowed diagnosing certain diseases and giving recommendations for their treatment.

In the middle of the last century, due to the fundamental work of W. McCullock, W. Pitts, F. Rosenblatt, a new strategy for creating intelligent systems - neural network technologies - emerged. The new strategy was different in that knowledge was entered into the created intellectual system not by the developer himself, but was acquired automatically in the learning process by examples of the behavior of the modeled domain. As a result, the opportunity has appeared for introducing the knowledge unknown to the system developers into the intellectual system. The latter circumstance has turned out to be especially important for such a scientific field as medicine, in which there are many "white spots", and the general knowledge is almost non-formalizable.

Currently there is an avalanche-like growth of publications devoted to the use of neural networks in medicine. Sound reviews [1-4] on the transfer of success, analysis of the possibilities and prospects for the use of neural networks in medicine have been published. The models of artificial neural networks have shown good results for the diagnosis of diabetes mellitus [5], cancer of the prostate [6], [7], pancreatic cancer [8], lung cancer [9], breast cancer [2, 3, 10] leukemia [11], hepatitis B [12], stroke [13], kidney disease [14, 15], Parkinson's [16] and Huntington's disease [17], for the early diagnosis of Alzheimer's disease [18], for planning radiation therapy for brain cancer [19], assessing the degree of mental retardation [20], and diagnosing diseases of the cardiovascular system [14, 21-28].

In many of these studies, for example [26, 29], neural network diagnostic systems are recommended to support clinical decisions of the physician, and in [9] - as a tool for preclinical diagnosis. It is noted in [15] that neural network systems allow reducing the time required for diagnostics, in [12] it is indicated that the use of neural networks allows optimizing the diagnostic process and avoiding erroneous diagnoses. [1] also states that neural networks help avoiding erroneous diagnoses, however, despite their wide application in modern diagnostics, they should be considered only as a tool to facilitate the final decision, for which the doctor is ultimately responsible. [8] notes the advantages of neural network diagnostics in comparison with physical diagnostics. In [13] it is proposed using neural networks to create mobile applications, to monitor the state of the body, for example, to diagnose strokes occurring during sleep.

It should be noted that in many mentioned publications, in addition to the term "diagnostics", the term "prognosis" is sometimes used, which is however understood only in the narrow sense of the word - as the "outcome of the disease" (that same diagnosis), and not the process developing in time. Thus, the work [21] reports on the use of neural networks for predicting ischemic heart disease, whereas in fact it is an early diagnosis of this disease. In [7], the prognosis of prostate cancer is reported, whereas the question is about determining the stage of development of this disease, i.e. about its diagnostics. Similarly, [29] reports on the use of neural networks to predict the risk of osteoporosis, [28, 30] - to predict the probability of organ survival during transplantation, in [31] - to predict bone fracture risk in patients with severe osteochondrosis, in [6] - to predict prostate cancer, [26] reported on the development of a neural network predicting the acute myocardial infarction within two weeks in patients with chest pain who have no infarction signs on the ECG.

The authors of [4] urge researchers to apply artificial intelligence methods not only for diagnostics, but also for optimizing treatment courses for patients, without explaining how to do it and not giving examples of such optimization.

Apparently, for the first time the possibilities of neural networks for predicting diseases as the processes developing in time, as well as for selecting optimal courses of treatment and lifestyle of patients leveling these diseases, were shown in the early publications of the authors of this article [32, 33]. In the same works, the examples of revealing new medical knowledge by the mathematical simulation method are provided. The results presented below continue these studies.

MATERIALS AND METHODS

The method of mathematical simulation and its possibilities

As follows from the above analysis of literature sources, neural networks are widely used to diagnose various kinds of diseases. However, our own experience in the use of neural network technologies in industry, economics, political science, sociology, ecology, psychology, criminology, pedagogy, medicine, and other fields [32-38] (www.PermAi.ru), as well as the richest experience of other researchers in other scientific fields, convincingly show that the possibilities of neural networks are much wider. The matter is that after training and testing the neural network becomes a mathematical model of the object under study, in the case of medicine it becomes a mathematical model of a person with his/her hereditary factors, physiological characteristics and diseases. This means that virtual computer experiments can be made using a mathematical model of the object under study (human) just as it is done in many other disciplines. Within the limits of mathematical error, the mathematical model behaves in the same way as the object under simulation itself, i.e. –the human, would behave. Therefore, in principle, neural networks, like classical mathematical models, can be used to study the patterns of objects under simulation. For example, by changing any or several input parameters (age, weight, habits, etc.), one can observe the behavior of output parameters - the degree of development of human diseases.

In technical disciplines, such studying of mathematical models is called the "freezing method", since all other input parameters characterizing the object under study remain unchanged during the computer experiment. In general, the method of mathematical simulation, in its classical form, has been fruitfully applied in many scientific branches for a long time. For example, we all know that the nuclear winter is a global drop in the temperature of the planet's surface caused by massive nuclear explosions that will result in perishing of all life on Earth. There is the opinion that it is the prospect of the nuclear winter that keeps politicians from unleashing a new world war.

However, no one has ever seen the nuclear winter!

The nuclear winter is just a result of virtual experiments [39] performed by mathematicians on mathematical models. This is the result of the so-called "scenario forecasting" - the forecast of what will happen if one or several input parameters of a mathematical model are changed, for example, on the ground surface at several points to set the parameters of heat-mass transfer processes such as those that occur during nuclear explosions. As a result, it turns out that the earthly civilization still exists due to scenario forecasts made by mathematicians in [39] and in a number of other similar publications.

Today, no complicated technical object is created without virtual computer experiments performed on a mathematical model thereof. It is due to such experiments that scientists and engineers know exactly how much the object they create will serve, what kinds of malfunctions it will have, how it will behave in difficult changing conditions, and what needs to be done to avoid troubles.

No physicist will ever think of experimenting on an atomic bomb, a nuclear reactor, a spacecraft, or a submarine. He/she will perform such experiments on mathematical models, in extreme cases - on *physical models*, i.e. on reduced and simplified copies of the full-scale object. However, in the XIXth century the method of experimentation on physical models (the method of physical modeling) was widely used. At the end of the XXth century, the method of physical modeling was almost completely replaced by a more progressive method of mathematical computer modeling.

Doctors, instead of looking at what the prescribed course of treatment will lead them virtually, on the mathematical model of the patient, put experiments directly on the full-scale object, i.e. - on the person. Based on their knowledge and experience, they prescribe medicines to the patient, observe him/her for a certain period of time, and if that does not help, prescribe them other drugs.

However, representatives of technical disciplines used the full-scale experimentation method even before the beginning of the XIXth century, and now its use is a rare anachronism. Therefore, we have the right to say that the methodological basis of medical science has lagged behind technical disciplines for more than a hundred years.

We can try to explain this lag by the fact that the method of mathematical simulation in its classical form, i.e. based on the solution of boundary value problems of mathematical physics, has long been inaccessible for application in the field of medical sciences in view of the extreme complexity of the simulation object - the human being. However, the methods of artificial intelligence allow us to overcome this barrier without resorting to solving complex boundary-value problems. They make it possible to build neural network mathematical models of patients based on statistical data alone and to carry out computer experiments on models - to virtually change the patient's lifestyle, to try various courses of treatment, to select medications, to watch on the computer screen what it will lead to in the nearest and remote perspective, i.e. - to perform *scenario forecasting.*

The issues of scenario forecasting and ways to overcome them

It should be noted, however, that scenario forecasting through the freeze of input parameters involves certain problems. The point is that in medicine, the input parameters of the object under simulation have complex correlation dependencies among themselves, and when one of the input parameters is changed, other parameters must also be changed according to these dependencies. For example, new symptoms, such as changes in the electrocardiogram, a change in the results of echocardiography and biochemical analyses, etc. appear with age, but such dependencies are unknown in advance.

Due to this, in [32, 33] the authors of this article proposed a method for overcoming these difficulties by combining the capabilities of two artificial intelligence technologies: neural networks and expert systems. Specifically: an original algorithm was proposed that allows adjusting the results of neural network scenario forecasts of the development of ischemic heart disease (IHD) with the help of knowledge embedded in the SCORE scale. Further dynamic diagnostic and prognostic models created with the help of this algorithm will be called the 1st type models.

The disadvantage of the algorithm proposed in [32, 33] is that in the general case it cannot be applied to other nosological forms, since the SCORE scale is designed and verified for IHD only. Unfortunately, there are no such developments for other diseases.

To eliminate this disadvantage, it is possible to try applying the sliding window method, which is usually used in time series forecasting problems [40]. To apply this method, the examples of the behavior of the object under simulation at time intervals must be available. In our case, such observations are the data on repeated patients' visits to the attending physician.

Let's say that we have a history of a patient's annual visits to the attending physician for *T* years. Then for each current visit $t \in [1, T]$ we can generate a vector of input parameters X_t, the elements of which are the current parameters of the patient. It is also possible to generate a vector of output parameters D_t with diagnoses of diseases. Following the sliding window method [40], we will form a training set taking the values of patient parameters in the current year X_t as input parameters, and the diagnoses for the following year D_{t+1} as output values. Thus, we get the following set of $T-1$ pairs of input and output vectors: $[(X_1, D_2), (X_2, D_3), ..., (X_t, D_{t+1}), ..., (X_{T-1}, D_T)]$. Repeating this operation for the entire multitude of patients, we will get many examples that can be used to train and test a neural network model designed to predict the development of the disease one year in advance.

To create a model predicting the development of diseases for n years ahead, the sets were formed in a similar way: $[(X_1, D_{1+n}), (X_2, D_{2+n}), ..., (X_t, D_{t+n}), ..., (X_{T-n}, D_T)]$. Dynamic diagnostic and prognostic models created by this method will be called the second type models.

The disadvantage of the second type models is that such models give an answer to the question of how the disease will progress if the patient does not change his/her lifestyle in subsequent periods of life and will not change the course of his/her treatment. In fact, after attending a physician, changes in the patient's lifestyle and treatment can occur, and in that case the forecasts will be different.

In order to take into account these changes, we will formulate examples of the training set, taking as input parameters the values of all patient data in the current year X_t, the values of the actual diagnoses in the same year D_t and those patient parameters that the doctor can influence, by giving his/her recommendations for a further way of life and treatment of the patient X'_{t+1}. Let's take the values of the diagnoses made in the next year D_{t+1} as output parameters of the model. Thus, we'll get a set of $T-1$ elements: $[(X_1, D_1, X'_2, D_2), (X_2, D_2, X'_3, D_3), ..., (X_t, D_t, X'_{t+1}, D_{t+1}), ..., (X_{T-1}, D_{T-1}, X'_T, D_T)]$.

Let's recall that here the input vectors are X_t, D_t, X'_{t+1}, and the output vector is D_{t+1}. Repeating this operation for the entire multitude of patients, we will get many examples that will be used to train and test a neural network model designed to predict the development of diseases taking into account the doctor's recommendations X'_{t+1}.

Note that compared to the previous model, the values of the actual diagnoses for the current year D_t were added to the input, which allows to take into account the current state of the patient in the model, since the development of the disease and, accordingly, the diagnosis in the next year depend on it. The current state also influences the effect the physician's recommendations will have on the patient. Moreover, here, to the model's input the recommendations of the physician X'_{t+1} are submitted, the compliance with which should also influence the diagnosis of the following year D_{t+1}.

To predict the development of diseases for the period of n years, sets for each patient are formed in a similar way: $[(X_1, D_1, X'_{1+n}, D_{1+n}), (X_2, D_2, X'_{2+n}, D_{2+n}), ..., (X_t, D_t, X'_{t+n}, D_{t+n}), ..., (X_{T-n}, D_{T-n}, X'_T, D_T)]$

Having broken the generated set of examples into the training and testing ones, having trained and tested the neural network, we will obtain a dynamic diagnostic and prognostic neural network model that takes into account the initial state of the patient, including the diagnoses made at the initial moment, as well as the expected treatment and lifestyle changes recommended by the physician. Dynamic neural network models created by this method will be called the third type models.

The disadvantage of the third type models is in the relatively high complexity of their creation and application, in particular, in the need to have current diagnoses D_t. Such disadvantages are unavailable for the following 4th option of the models' creation. The essence of this option is that from the very beginning we are striving to use, if possible, a small number of uncorrelated input parameters, leaving many other input parameters "behind the scenes". For example, when developing a neural network system for diagnosing and forecasting the development of cardiovascular diseases, we fundamentally refuse to use such important data for the diagnosis as the results of a biochemical blood test, electrocardiography, coronary angiography, and many specific methods for verifying diseases. Instead, we enter the maximum possible number of parameters that characterize the patient's body: sex, age, eye color, hair color, blood group, presence of a transverse fold on the earlobe, place and time of birth, genetic parameters, heredity, etc. We inform the neural network about the environment in which the patient lives, how he/she feeds, what way of life he/she has, the existence of his/her brothers and sisters, his/her profession, the presence of bad habits, physical education and sports; we report information about previously transmitted diseases, information about the presence of diseases in blood relatives, and also we inform about the minimum number of the patient's complaints. Sometimes, with the skillful selection of input parameters, these data are sufficient to teach the neural network to diagnose certain diseases with an acceptable degree of accuracy.

Once again, we note that such mathematical models do not include data from many special types of survey as input parameters. Many patient complaints that have high correlation with the diagnosis made are also not included. Therefore, in the subsequent computational experiments with the application of the freezing method, there are no restrictions on these data remaining behind the scenes; i.e. they "do not freeze". Thus, we overcome the problem of the freezing method - we do not break the interdependence between the input parameters that influence the diagnosis of the patient, and the neural networks become suitable for performing virtual computer experiments of scenario forecasting.

The disadvantage of the 4th type neural network models is that only researchers who are well versed in the subject area and have extensive experience in machine learning can successfully create such models. But even in this case, success is not guaranteed.

Diagnostic and prognostic systems and their testing

Taking into account the above, we created a neural network diagnostic and prognostic system consisting of a set of the 4th type neural network models, each of which corresponded to various nosological forms of cardiovascular diseases and included 27 input neurons to input the parameters characterizing general information about the patient, history and his/her lifestyle, as well as the minimum number of patient complaints. To train neural networks, numerous data about 980 patients of the Department of Emergency Cardiology of the City Clinical Hospital No. 4 in Perm were used.

Generation of neural networks, their training, optimization and tests were carried out in the neuro package [41] for each nosological unit according to the technique [34]. The best were the perceptron type neural networks with one hidden layer containing one to four sigmoid neurons.

After training, the neural networks were united by a user interface into a single neural network diagnostic and prognostic system. The user interface is designed so that the results of the system operation are represented graphically in eight columns, the height of each of them would reflect the degree of development of the relevant nosological form of the cardiovascular disease, as shown in Fig. 1-10.

The diagnostic and prognostic properties of the system were checked on a test set of 250 data on patients not included in the training set. The relative root-mean-square error of testing neural networks was estimated using the formula

$$\varepsilon = \frac{\sqrt{\dfrac{\sum_{i=1}^{I}(d_i - y_i)^2}{I}}}{\max(d_i) - \min(d_i)} 100\%, \quad (1)$$

where I is the number of elements of the test set, d_i is the severity of the disease diagnosed by the physician, and y_i is the severity of the disease diagnosed by the neural network. The ε value was 30% for myocardial infarction (corresponding to sensitivity of 81.4% and specificity of 90.0%), 22% for stable angina, 18% for unstable angina, 20% for coronary heart disease, 12% for hypertension, 22% for arrhythmia and heart block, 12% for chronic heart failure, 35% for acute heart failure.

It should be noted that the accuracy of diagnosing using the diagnostic and prognostic system built on the 4th type model could be improved by introducing additional input parameters, for example, by adding data of electrocardiography, echocardiography, coronaroangiographic studies, current general and biochemical blood analysis, etc., as it was done in our early studies [32, 33]. Nevertheless, in such a case neural networks would not be suitable for scenario forecasting. These additional input parameters would have to be "frozen", which is contrary to reality. For example, with a virtual increase in age, the parameters of the biochemical blood test, the data of echocardiographic studies, etc., must necessarily change.

Similarly, diagnostic and prognostic systems based on models 1, 2 and 3 were constructed. For each system, using the formula (1), the errors of diagnosis on test sets were calculated. The average results of the testing error ε for all four diagnostic and prognostic systems on the example of IHD are given in Table 1.

Table 1. Average errors in testing diagnostic and prognostic systems based on IHD

1st type models	2nd type models	3rd type models	4th type models
4.7%	7.5%	5.5%	20%

As can be seen from the table, diagnostic and prognostic systems based on the 4th type models have the greatest inaccuracy, which is explained by the absence of many important input parameters, such as biochemical blood test parameters, data of echocardiographic and coronarography studies, etc.

RESULTS AND DISCUSSION

Virtual computer experiments were performed on mathematical models of three patients.

Patient 1. The man aged 50 (born on 09.05.1967), height - 177 cm, weight - 80 kg, blood type - two, Rh factor positive, smoking, not doing physical exercises, there are heart diseases in blood relatives, no hypertension, no diabetes, no cerebral blood flow violations, no diagnosis of heart disease, no cardiac surgery, thrombophlebitis, no chest pains, complaining of shortness of breath with physical exertion, no asthma attacks at night, heartbeat, no sensations of interruptions in the work of the heart, no swelling of the limbs and face, not complaining of dizziness and headaches.

Patient 2. The woman aged 39 (born on 20.11.1977), height - 160 cm, weight - 60 kg, blood type - first, Rh factor positive, smoking, not doing physical exercises, no heart diseases in blood relatives, no hypertension, no diabetes, no cerebral blood flow violations, no diagnosis of heart disease, no cardiac surgery, no varicose disease or thrombophlebitis, no pains in a thorax, no shortness of breath, no asthma attacks at night, no palpitations, no sensations of faults in work of heart, having edemas of the face, complaining of frequent dizziness and headache.

Patient 3. The man aged 50 years (born on 15.08.1966), height - 180 cm, weight - 75 kg, blood type - fourth, Rh factor negative, smoking, not doing physical exercises, with heart diseases in blood relatives, no hypertension, no diabetes, no cerebral blood flow violations, earlier diagnosis of heart disease, no cardiac surgery, thrombophlebitis, no chest pains, complains of dyspnoea at rest, there are no attacks of choking at night, no palpitations, having sensations of interruptions in the work of the heart, having edemas of the extremities, complaining of frequent dizziness and headache.

After entering the parameters of patients, the neural network system has made the diagnoses presented in graphical form in Fig. 1, *a* - to patient No. 1, in Fig. 1, *b* - to patient No. 2, in Fig. 1, *c* - to patient No. 3.

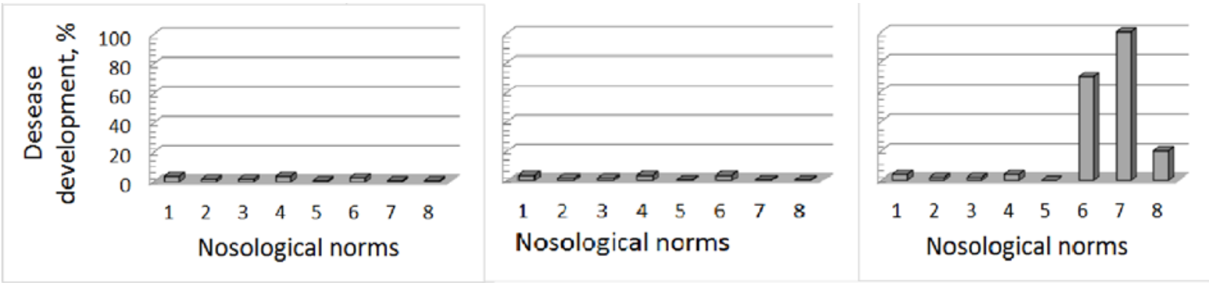
As can be seen from the picture, in patients No. 1 and No. 2 the system did not reveal the risks of cardiovascular diseases, whereas in patient No. 3 the system diagnosed: cardiac arrhythmia and blockade - 70%, chronic heart failure (CHF) - 100%, acute heart failure (AHF) - 20%.

In Fig. 2 in a similar form, the results of scenario forecasting of the development of diseases are given, if the age of patients has increased by 30 years, and the weight - by 20 kg. All other parameters of patients were kept unchanged. As can be seen from the picture, in patient No. 1 the system forecasted the appearance of a risk of arrhythmia and heart block - 70% and the risk of CHF - 100%. Patient No. 2 had no cardiovascular disease risks, and in patient No. 3 the system predicted the risk of arrhythmia and heart block - 70%, the risk of CHF - 100%, and the risk of AHF - 60%.

Fig. 3 shows the results of scenario predictions of the development of cardiovascular disease provided that in addition to increasing age and weight, patients were ill with diabetes mellitus. As can be seen from the figure, in patient No. 1 diabetes mellitus stimulated the appearance of a 98% risk of stable angina, 91% risk of unstable angina, and a 98% risk of coronary heart disease. Risks of arrhythmia and cardiac blockade, as well as CHF remained at the same high level - 70% and 100%, respectively. In patient No. 2, diabetes did not cause any risk of cardiovascular disease, while in patient No. 3 diabetes led to an increase in the risk of AHF to 75%.

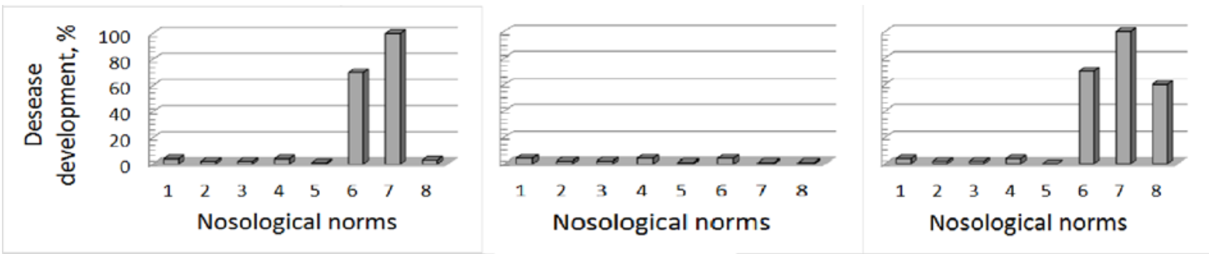
In Fig. 4 the results of forecasting are different in that the diagnosis of diabetes mellitus has been virtually removed, and instead of it hypertensive disease has been added. This forecast corresponds to the fact that during the diagnosis (30 years ago) it was recommended to the patients to abstain from sweets, and they did not follow the arterial pressure. As can be seen from the figure, the addition of hypertension instead of diabetes mellitus in patient No. 1 did not change the pattern of scenario predictions, in patient No. 2 a 26% risk of CHF appeared, and in patient No. 3 the risk of AHF decreased from 75% to 30%.

In Fig. 5 the results of scenario forecasting differ in that, among other things, patients have been regularly engaged in physical exercises or light sports all this time (for 30 years). As can be seen from the figure, in this case, in patient No. 1, the risk of stable angina would decrease from 98% to 2%, the risk of unstable angina would remain at the same level, the risk of coronary artery disease would decrease from 98% to 91%, the risk of arrhythmia and blockade of the heart would decrease from 70% to 4%. In patient No. 2, CHF would decrease from 26% to zero, and in patient No. 3 the risk of AHF would decrease from 30% to 8%.



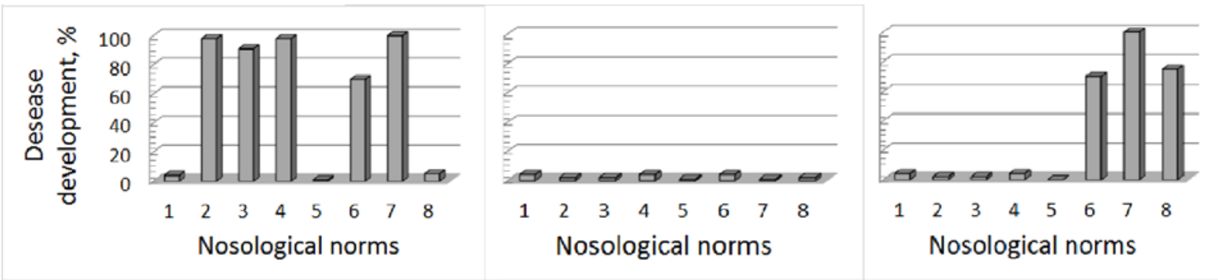
a b c

Fig. 1. Degrees of development of diseases diagnosed by the system: a – to patient No. 1, b – to patient No. 2, c – to patient No. 3. Risks of diseases: 1 - myocardial infarction, 2 - stable angina, 3 - unstable angina, 4 - ischemic heart disease, 5 - hypertension, 6 - arrhythmia and heart block, 7 - chronic heart failure, 8 - acute heart failure



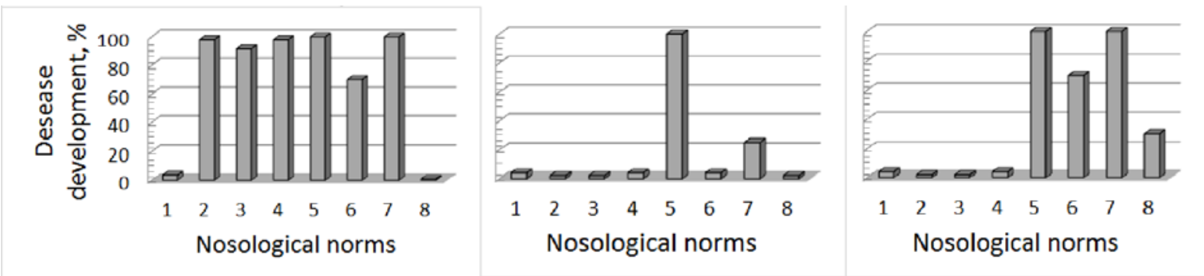
a b c

Fig. 2. The same provided that the age of the patients has increased by 30 years, and the weight has increased by 20 kg



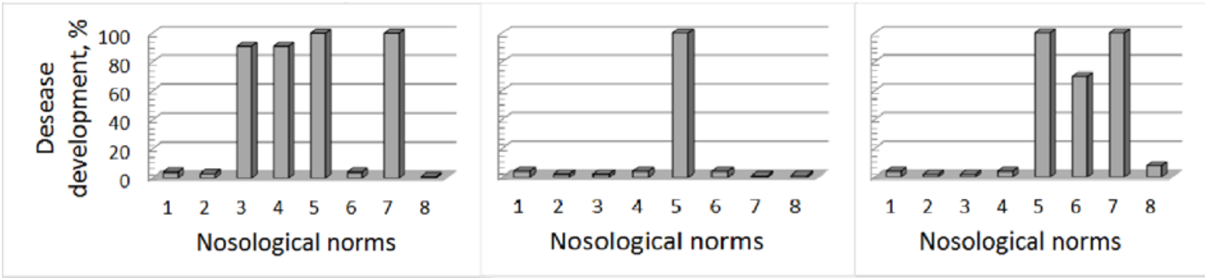
a b c

Fig. 3. The same provided that in addition to increasing age and weight, patients acquired diabetes mellitus



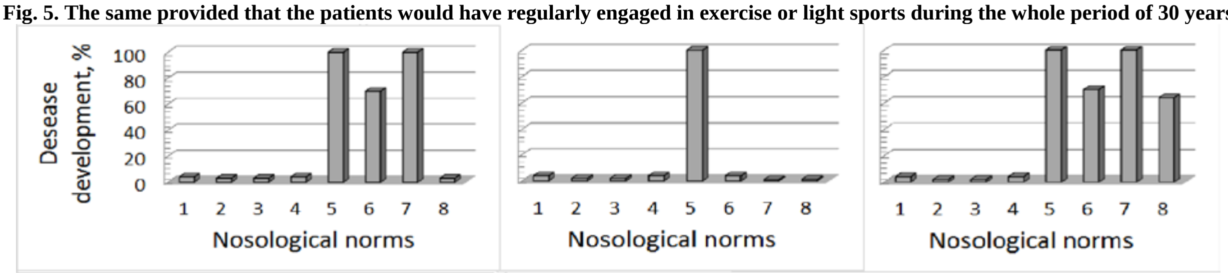
a b c

Fig. 4. The same provided that instead of diabetes, patients acquired hypertensive disease



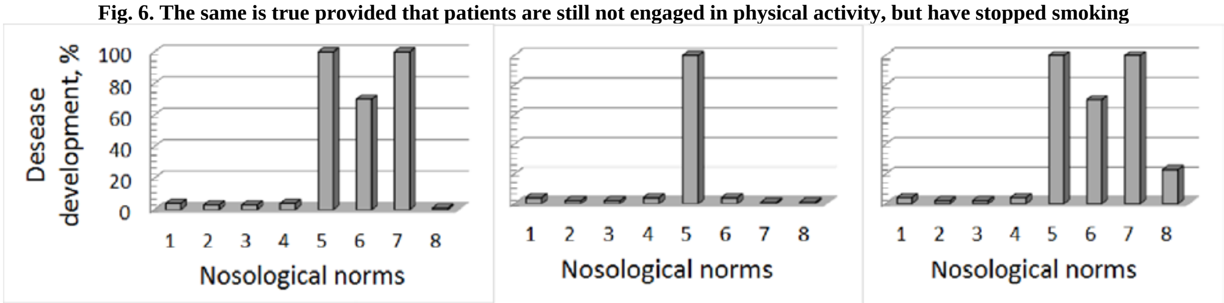
a *b* *c*

Fig. 5. The same provided that the patients would have regularly engaged in exercise or light sports during the whole period of 30 years



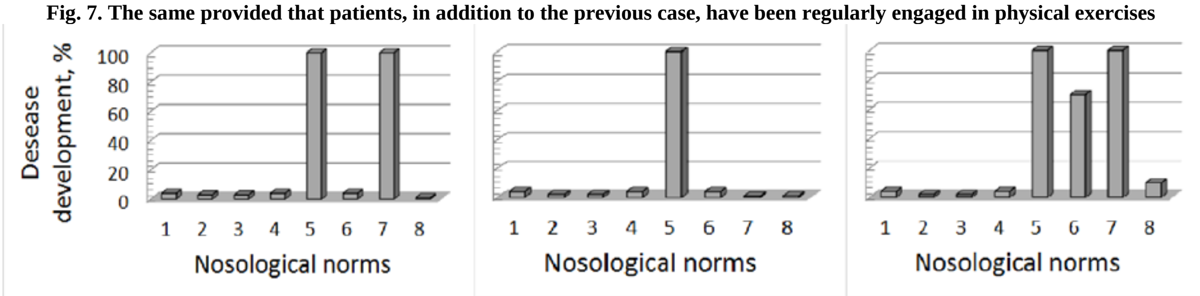
a *b* *c*

Fig. 6. The same is true provided that patients are still not engaged in physical activity, but have stopped smoking



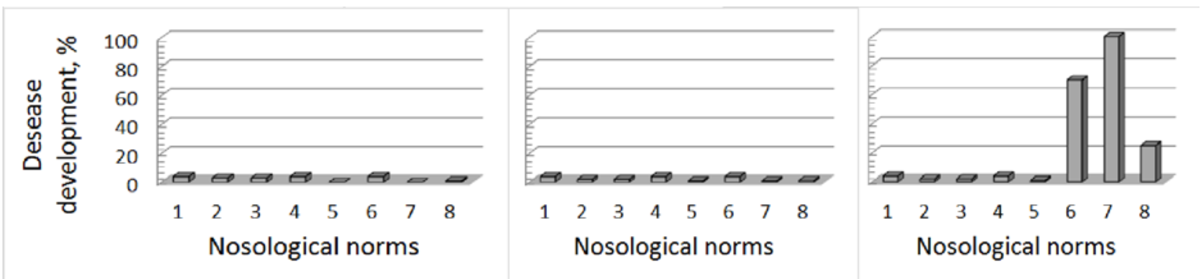
a *b* *c*

Fig. 7. The same provided that patients, in addition to the previous case, have been regularly engaged in physical exercises



a *b* *c*

Fig. 8. The same is true provided that patients would reduce their weight by 20 kg, i.e. would return to their original weight



a *b* *c*

Fig. 9. The same is true provided that patients maintain their blood pressure as normal

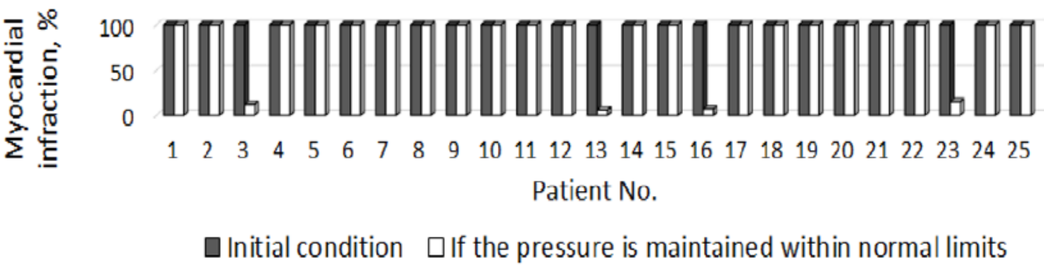


Fig. 10. Scenario forecast for twenty-five patients with myocardial infarction if they regularly maintain blood pressure within normal limits

Fig. 6 provides the results of scenario forecasting on the assumption that patients are still not engaged in physical exercises, but stop smoking. In this case, patient No. 1 would have zero risk of both angina and IHD, but the risk of arrhythmia and heart block would remain at 70%, as in Fig. 4. In Patient No. 2, the pattern of scenario forecasting would be preserved, as in Fig. 5, i.e. for him to stop smoking or to do physical exercises instead equally positively affects the state of the cardiovascular system, namely, the risk of CHF in both options of the patient's behavior would be avoided. For patient No. 3, the stopping of smoking will lead to an increase in AHF from 8% to 63%. It is not recommended to stop smoking for such patient. Apparently, the habit of smoking allows him to level out the resulting stresses, which has a positive effect on the state of his cardiovascular system, in particular, on the predisposition to AHF.

The results shown in Fig. 7 were obtained on the assumption that the patients have been still engaged in regular physical exercises (despite the fact that they stopped smoking). In this case, the forecasting diagnoses of the first two patients did not change, and patient No. 3 managed to reduce the risk of AHF from 63% to 22%. Let us recall that when patient No. 3 was engaged in physical exercises and still smoked, the risk of AHF was only 8% (see Figure 5). Hence, it follows that in order to minimize the risk of AHF, it is useful for this patient to do physical exercises and not to stop smoking.

Fig. 8 presents the results of scenario forecasting on the assumption that patients have reduced their weight by 20 kg, that is, returned to their original weight, which they had 30 years ago. In this case, the risk of cardiac arrhythmia and heart blocking of the first patient would decrease to 4% from 70%, the risk of cardiovascular disease of the second patient would remain the same, and the risk of the third patient's AHF would decrease from 22% to 10%.

Fig. 9 presents the results of scenario forecasting on the assumption that patients would maintain normal blood pressure. As can be seen from the figure, this would allow the first patient to reduce the risk of CHF from 100% to zero. The health indicators of the second patient would remain unchanged, and in the third patient, on the contrary, the risk of AHF would increase from 10% to 25%.

In conclusion, we point out that experiments on the prediction of the development of diseases (Figures 1-9) in different options were performed using diagnostic and prognostic systems based on the third and fourth type models, and gave similar results.

KNOWLEDGE ELICITATION

As noted earlier, neural networks in the learning process extract regularities of simulated subject areas, encode them in the form of synaptic connections, and use this knowledge, in particular, when diagnosing and predicting the appearance and development of diseases. However, such knowledge is non-verbal in the sense that it is very difficult to imagine it in a form that is easy to understand. As a result, our attempts to understand and explain, for example, why regular intake of drugs normalizing blood pressure, according to the results of the forecast in Fig. 9, allowed the first patient to reduce the risk of CHF from 100% to zero, the health of the second patient remained unchanged, and the third patient, on the contrary, increased the risk of AHF from 10% to 25%. We can only state that neural networks have done this conclusion by processing a large number of patient parameters, and among these sets we cannot see the dependencies available for human perception.

Apparently, such direct verbalization of medical knowledge, detected with the help of neural networks, will be the subject of future research. In the meantime, we will use an indirect method of verbalizing neural network knowledge, which is as follows.

Let us take 200 real patients with myocardial infarction, suffering from hypertension, and see what would happen if they regularly maintain their blood pressure within normal limits. Calculations made with our diagnostic and prognostic system showed that in this case, twenty out of two hundred patients under study could avoid a heart attack. Hence it can be concluded that regular intake of medications normalizing blood pressure reduces the risk of myocardial infarction in about 10% of patients.

The graphical interpretation of the computational experiment is shown in Fig. 10. Here, the dark color shows the diagnoses made to the patients before the virtual adjustment of blood pressure to normal, and white - after bringing the blood pressure back to normal. For readability, the sampling is limited to twenty-five examples.

Further experiments carried out using the same procedure showed the following results:

- the presence of poor heredity increases the risk of myocardial infarction in 6.3% of patients;
- a decrease in the mass index to 21.75 reduces the risk of myocardial infarction in 12.6% of patients;
- regular morning exercise in 18.8% of patients leads to an increased risk of myocardial infarction;
- smoking increases the risk of arrhythmia and heart block in 3.3% of patients;
- a change in body mass index does not affect the risk of arrhythmia and heart block in 100% of patients;
- bringing blood pressure to normal in patients with arrhythmia and heart block does not reduce the risk of this disease in 100% of patients.

In conclusion, it should be noted that the computational experiments were conducted every time on two hundred real patients of the Department of Urgent Cardiology of the Perm City Clinical Hospital (Russia). Therefore, it is natural to assume that the results obtained relate to the population of this region. For other regions of the world, the results are likely to be somewhat different.

CONCLUSIONS

The article shows the possibility of creating neural network medical systems that, in addition to diagnosis, allow performing long-term forecasts of the development of diseases, predicting the occurrence of new diseases in future periods of the patient's life, selecting the optimal way of life for patients, methods of prevention and treatment of diseases, and identifying medical knowledge.

The results of virtual computer experiments cited in the article in most cases do not contradict the "common sense" of an experienced diagnostician. However, there are exceptions. Thus, the recommendation to stop smoking to patient No. 3 may lead to an increase in the risk of AHF, as shown in Fig. 6, *c*. It is not always useful to maintain normal blood pressure, since this also can lead to an increase in the risk of AHF, as it turned out in Fig. 9, *c*.

In general, the results of computer simulation have confirmed the conclusion previously obtained by mathematical modeling [32, 33] that recommendations for the prevention and treatment of cardiac patients should be given strictly individually, taking into account the physiological characteristics of the patient's body. While for some patients such common recommendations as "to limit the use of sweets", "to stop smoking", "to take drugs that reduce blood pressure", "to regularly exercise", etc., are really helpful, they can cause harm to others. The proposed diagnostic and prognostic system allows identifying such non-standard patients and avoiding erroneous recommendations.

A demonstration prototype of the developed diagnostic and prognostic system is available in the "Projects" section on the website of the Perm Branch of the Scientific Council on the Methodology of Artificial Intelligence of the Russian Academy of Sciences www.PermAi.ru, and can be used for the population preclinical diagnosis, to support medical decisions, to identify new medical knowledge, as a simulator in medical universities and advanced training centers, etc.

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