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INTELEGENCE DIAGNOSTIC SYSTEM OF LIVER FIBROSIS STAGES

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Abstract**—***The necessity of constructing an intelligent system for diagnosing stages of liver fibrosis is determined, for which the values of the parameters characterizing the functioning of the liver are determined. Magnetic resonance imaging is considered as the main medical equipment used for diagnosis. A structural diagram of the diagnostic system is developed, which includes a tomogram processing subsystem and a decision-making subsystem. As a basic element of the tomogram processing subsystem, a convolutional neural network (Residual Network) is used, the training of which is carried out using the Transfer Learning algorithm. As the parameter that determine the stage of liver fibrosis, the image texture is used. The decision support subsystem is built on the basis of fuzzy neural networks. Examples of the system when determining the stages of fibrosis are given.*

Index Terms—Intelligent system; stages of liver fibrosis; magnetic resonance imaging; convolution neural network; Transfer Learning algorithm; texture; fuzzy neural networks.

I. INTRODUCTION

In 2018, the global market for AI technology for healthcare reached $ 1.4 billion, according to Zion Market Research. By 2025, the indicator is expected to grow to $ 17.8 billion, and the cost of such decisions will increase by about 43.8% annually.

Most of all, medical artificial intelligence (machine learning, context-sensitive computing, natural language processing, computer vision, speech recognition) is spent in North America. The leadership is due to the fact that this region is represented by technology giants such as Microsoft, IBM, Google, Nvidia, Amazon, Intel, General Electric and Xilinx. In addition, mergers and acquisitions, large partnerships, and the launch of important products are frequent in North America.

In Europe, in 2016, the market volume for artificial intelligence was measured at $ 320 million, by 2019, it amounted to $ 1.61 billion. At the same time, 21% of medical institutions in Europe plan to purchase AI tools, according to data from the European eHealth community, released in April 2019.

One of the main reasons for the demand for AI products in medicine is the shortage of doctors. According to the World Health Organization, by 2019, 57 countries are missing approximately 2.3 million nurses and doctors [2].

Each medical image, examination protocol and medical history contains information that allows you to accurately diagnose and prescribe treatment. Unfortunately, even experienced doctors do not always see the full picture of the disease, because the data in the medical record are not structured, and the medical history may be too voluminous. Their performance is also affected by fatigue and, in some cases, a lack of knowledge in narrow areas.

Some diseases, for example, oncological ones, can be defeated if in time to recognize non-obvious symptoms and begin treatment. According to Google, one in ten patients suffers from a misinterpretation of medical information.

Agency Frost & Sullivan notes that artificial intelligence technologies increase the accuracy of diagnosis by 30–40%, while the cost of medical care is reduced by half.

II. LIVER FIBROSIS

In many developing countries, liver disease is among the top five causes of death. Diagnosis and monitoring of the dynamics of chronic liver diseases is one of the most urgent tasks of modern hepatology. Liver fibrosis is a local or diffuse increase in the amount of connective tissue, extracellular matrix (collagenous fibrous tissue in the perisinusoidal space) and the main pathway for the progression of chronic diffuse liver diseases. In the early stages of fibrosis, there are no clinical manifestations, and only with a histological examination of the biopsy reveals excessive accumulation of connective tissue. In the future, fibrosis leads to the formation of regenerate nodes, vascular anastomoses – the formation of liver cirrhosis. Noncirrhotic liver fibrosis is rare and is not considered in this paper.

The early stage of fibrosis is difficult to diagnose, as often it is asymptomatic.

Liver fibrosis is a pathological process characterized by proliferation of connective tissue among hepatocytes. Liver cirrhosis is a broader concept, since it includes not only the proliferation of connective tissue structures in the liver, but also a change in its architectonics, that is, the liver beams lose their normal structure, regenerative nodes appear.

The initial stage of liver damage in fibrosis is characterized by an increase in liver size. In the future, there is a decrease in the level of leukocytes, platelets and red blood cells. As a result, the patient has anemia and thrombocytopenia. A sign that the disease goes to the stage of cirrhosis is an enlarged spleen, varicose veins in the esophagus and hemorrhages of them.

The severity of fibrosis in chronic liver disease reflects the long-term prognosis and, therefore, the need and urgency of treatment. Fibrosis of the liver has 5 degrees (stages): F0, F1, F2, F3, F4 (cirrhosis).

For quantitative assessment, the METAVIR fibrocirrhotic change scale is usually used, which distinguishes 5 stages of the disease: F0 – absence of fibrosis (healthy liver tissue), F1 – portal and periportal fibrosis, F2 – portoportal septa, F3 – port-central septa, F4 – CPU (false slices).

Although liver biopsy is the standard of reference for diagnosis and staging of liver fibrosis, it is an invasive procedure with possible complications such as hemorrhage, hospitalization in 3% of cases, and a fatality rate of 0.03%. Furthermore, liver biopsy captures only a tiny fraction of the liver (roughly 1/50,000 th), leading to sampling variability. So, it is necessary to collect much information, which connected with fibrosis and analize it.

First, it is history of patient:

- age;
- gender;
- burdened heredity;
- chronic diseases;
- alcohol (with regular excessive consumption of drinks containing ethyl alcohol, damage to liver cells (hepatocytes) develops, which leads to the development of alcoholic liver disease. By excess is meant 30 grams – for men and 20 grams – for women per day. Damaged hepatocytes cannot perform their functions and are replaced by adipose and connective tissue);
- malnutrition ("non-alcoholic fatty liver dystrophy", "fatty hepatosis", since the main changes in the liver with this pathology are the replacement of hepatocytes with fat cells. The causes of fatty degeneration of the liver, not associated with alcohol, are increased body weight, obesity, and diabetes. The focus of these factors can be called metabolic syndrome – a condition associated with increased body weight, impaired metabolism in the body of glucose and fats);
- viral infections (Among the infectious diseases of the liver, viral hepatitis is most often found, which, according to the variety of pathogen, are divided into A, B, C, D, G and E. Hepatitis A virus is a causative agent of Botkin's disease, viral jaundice. After recovery, the liver is fully restored, chronic hepatitis is not formed. The above is true, with rare exceptions, for hepatitis E. Hepatitis B, C, D, and G not only irreversibly damage hepatocytes when they enter the liver, but also cause the development of chronic hepatitis, which, if untreated, leads to cirrhosis);
- medicines (about 1,000 drugs, out of the many currently registered, can cause liver damage. These include: non-steroidal anti-inflammatory drugs; antihypertensive drugs (metoprolol, atenolol, verapamil, enalapril), amiodarone; anti-TB drugs (isoniazid); aminoglycoside antibiotics (streptomycin, rifampicin); antifungal drugs (ketoconazole, fluconazole).

Symptoms of the fibrosis are:

- weakness;
- increased fatigue;
- pain in the right hypochondrium;
- jaundice staining of the skin and mucous membranes;
- itchy skin;
- change of mood;
- increase in the size of the phalanges of the fingers;
- weight loss;
- jaundice staining of the skin and mucous membranes;
- constant shortness of breath;
- swelling of the skin.

In the list of tests shown for suspected liver disease, a biochemical blood test is in the first place. Tests for liver enzymes can be part of a biochemical blood test or performed separately if serious deviations from the norm (reference values) are detected (Tables I and II).

TABLE I. THRESHOLD VALUES OF PLATELETS, ALBUMIN AND TNF-A FOR DIFFERENTIATION OF STAGES OF LIVER FIBROSIS

Stage Fibrosis of the Liver	Indicator Values		
	Platelets, 10^9/l	*Albumenc, g/l*	*Tumor Necrosis Factor -α, pg/ml*
from F0 to F1	282	47.3	1.9
from F1 to F2	243	45.6	2.4
from F3 to F4	200	44.1	2.8

TABLE II. BIOCHEMICAL BLOOD TEST OF THE PATIENT

Name / Metric	Result	Reference values
Alanine aminotransferase (ALT)	59 Un/l	0–41
Bilirubin Common	6.70 micromole /l	0.00–21.00
Cholesterol Common	5.73 mmol /l	2.90–5.20
Alaninamino Transferase (ALT)	20 Un/l	0–41
Triglycerides	1.36 mmol /l	0.00–2.25
Bilirubin Common	4.80 micromole /l	0.00–21.00
Gamma-glutamyltranspeptidase (gamma-GT)	31 Un/l	10–71
Apolipoprotein A-1	1.64 g/l	1.04–2.02
Alpha-2-macroglobulin	5.34 g/l	1.19–2.54

Today, significant successes have been achieved in the field of magnetic resonance technology and the high accuracy of magnetic resonance imaging (MRI) has been demonstrated as non-invasive quantitative methods for evaluating liver fibrosis. So as a technical mean of the proposal diagnostic system will be used MRI [1].

III. SELF-LEARNING INTELLIGENT SYSTEMS

Among the expert medical systems, a special place is occupied by the so-called self-learning intelligent systems (SIS). They are based on methods for automatically classifying situations from real practice or on teaching methods using examples. The most striking example of SIS is artificial neural networks. Artificial neural networks (ANNs) are a structure for processing cognitive information based on modeling brain functions. The basis of each ANN is relatively simple, in most cases of the same type of elements (cells) that mimic the work of brain neurons. Each neuron is characterized by its current state by analogy with nerve cells in the brain that can be excited or inhibited.

An artificial neuron has a group of synapses – unidirectional input connections connected to the outputs of other neurons, and also has an axon – an output connection of this neuron, with which a signal (excitation or inhibition) arrives at the synapses of the following neurons.

An ANS is characterized by the principle of parallel signal processing, which is achieved by combining a large number of neurons into the so-called layers and connecting neurons of different layers. Theoretically, the number of layers and the number of neurons in each layer can be arbitrary, but in fact it is limited by computer resources. In the general case, the more complex the ANN, the larger the tasks subject to it.

The most important difference between ANNs and other forecasting methods is the ability to design expert systems by a specialist physician himself, who can transfer his individual experience and the experience of his colleagues to a neural network or train the network on real data obtained by observation. Neural networks are able to make decisions based on the hidden patterns revealed by them in multidimensional data. A positive distinguishing feature of ANNs is that they are not programmable, i.e. they do not use any inference rules for making a diagnosis, but are trained to do this with examples. In some cases, ANNs can demonstrate amazing properties inherent in the human brain, including finding patterns in confusing data. Neural networks have found application in many areas of technology, where they are used to solve many applied problems: in space, automotive, banking and military, insurance, robotics, data transfer, etc. Another, equally important property of a neural network is the ability to learning and summarizing the knowledge gained. The network has the features of so-called artificial intelligence. Trained on a limited set of 11 training samples, it summarizes the accumulated information and produces the expected response in relation to data not processed in the learning process.

IV. THE STRUCTURE OF THE PROPOSED MEDICAL DIAGNOSTIC SYSTEM

The block diagram of the intelligent diagnostic system is shown in Fig. 1.

The information from the patient enters the system through the interface and includes data according to the Section II. Video images in digital form enter the blocks of filtering and elimination of geometric distortions to eliminate the influence of noise. After that, the video image sent the anomalous region selection block, which is implemented on the basis of the convolutional neural network (CNN) (see Section V). Evaluation of signs that determine the type of liver pathology by the results of MRI is executed in anomalous region estimation block.

After that, the video image is sent to the anomalous region selection block, which is implemented on the base of the CNN (see Section V).

Then the parameters of the signs obtained from the image analysis are compared with the normal state of the organ being examined and with the pathological changes that are in the database [3]. It stores survey and sample data, pre-generated using the statistical processing block, and signs of diseases. This block interacts with the decision support block. Based on the data obtained from the information block on the set of pathogenetic factors, the multi-factor analysis block allows you to create regression equations for them [4]. Then, using the decision rules from the block of the same name, the recommended solution is formed.

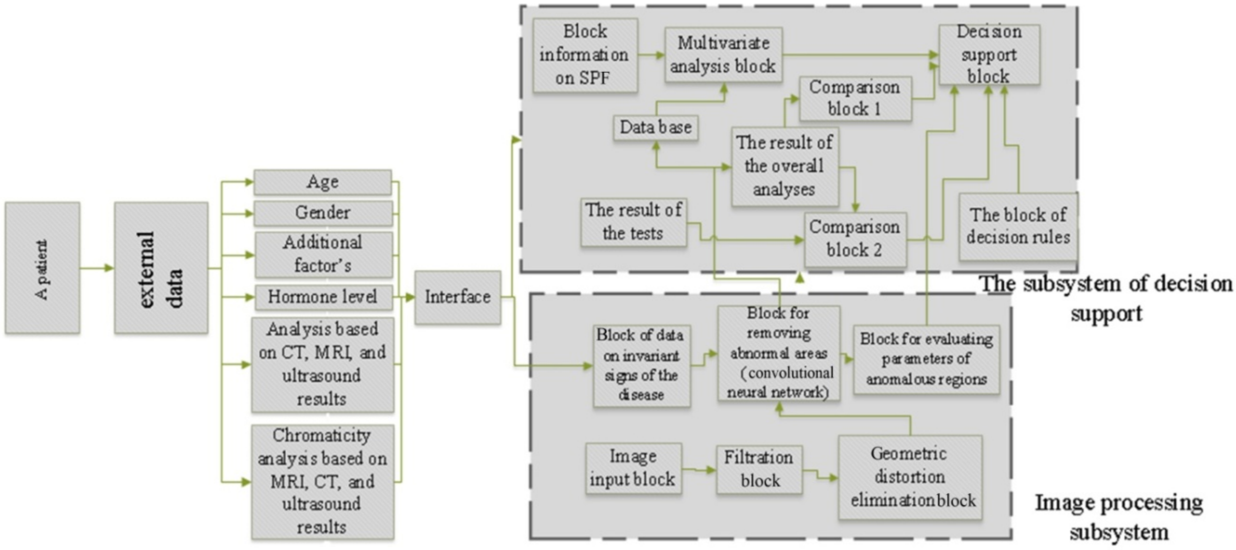

Fig. 1. Block diagram of intelligent diagnostics

The decision supportblock generates and displays special data on the monitor in a convenient form for the doctor, as well as evaluates their information reliability and makes recommendations to the doctor for making a diagnosis, taking into account the factors that affect the disease.

V. HIGH-PERFORMANCE CONVOLUTIONAL NEURAL NETWORKS

The convolutional neural network is a special architecture of the artificial neural network imitating the features of the visual area of the cerebral cortex [5]. In case of MRI image of liver fibrosis it's necessary to process the texture of image.

There are some principal types of CNNs used for image classification: AlexNet, VGG16, ResNet, CycleGAN, UNet, Mask RCNN.

AlexNet is a convolutional neural network that has had a great influence on the development of machine learning, especially computer vision algorithms. AlexNet contains eight layers with weights. The first five of them are convolutional, and the remaining three are fully connected.

VGG16 is a convolutional neural network model, which is an improved version of AlexNet, in which large filters (sizes 11 and 5 in the first and second convolutional layers, respectively) are replaced by several 3x3 filters, one after the other. Unfortunately, the VGG network has two serious disadvantages: 1) a very slow learning speed; 2) the network architecture itself weighs too much (there are problems with the disk and bandwidth). Despite the disadvantages, this network is an excellent building block for training, as it is easy to implement.

ResNet is an abbreviation for Residual Network. The ResNet model has fewer filters and less complexity than VGG networks. ResNet converges faster than its simple analog, while deeper ResNet achieves better learning results than an non-deep network.

CycleGAN is a type of generative adversarial network used to carry image style. CycleGAN can be trained to convert images from one domain (e.g. Fortnite) to another, such as PUBG.

UNet is considered one of the standard CNN architectures for image segmentation tasks, when it is necessary not only to determine the entire class of an image, but also to segment its areas by class, i.e. create a mask. The network architecture is a sequence of layers that first reduce the spatial resolution of the image, and then increase it by first combining it with the image data and passing through other layers of the convolution. Architecture the convolution network UNet can be used not only for segmentation, but also for detecting objects in images.

Mask RCNN – a network with this architecture allows you to highlight the contours (masks) of different objects in photographs, even if there are several such objects, they have different sizes and partially overlap. The network is also capable of recognizing the poses of people in the image. Mask RCNN develops the Faster RCNN architecture by adding another branch that predicts the position of the mask covering the found object, and thus solves the instance segmentation problem.

Since in this work it is necessary to classify the texture of liver tissue, high demands are placed on the accuracy of solving the classification problem [6].

The better results are given by ResNet, which is based on the so-called residual block (Fig. 2), with a shortcut connection through which data passes without changes. The Res block is a series of convolutional layers with activations that convert the input signal x to $F(x)$. A shortcut join is an identity transformation $x \rightarrow x$. The architecture of the ResNet represented on Fig. 3.

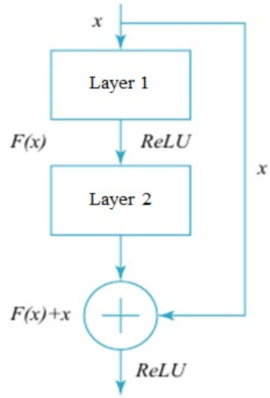

Fig. 2. The residual block of the ResNet architecture

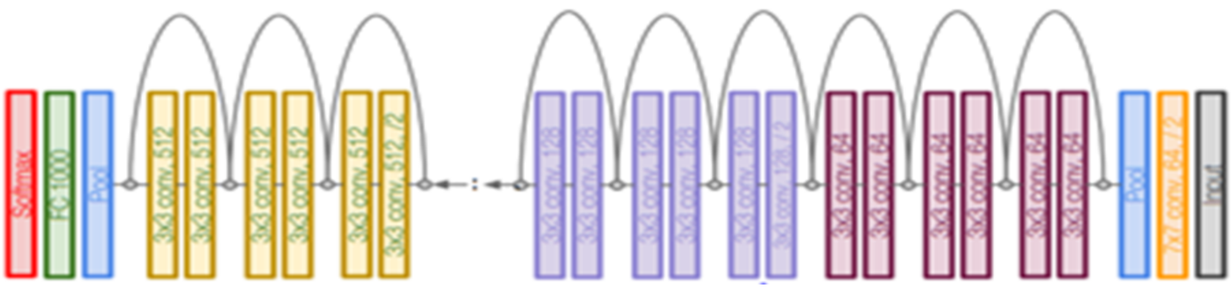

Fig. 3. Architecture of the ResNet

Using the ResNet architecture, it was possible to train a neural network with a depth of 18 layers (against the three-layer network used in the initial stages of work) with achieving acceptable recognition results simultaneously for 10 classes (five are sufficient for recognizing liver fibrosis) with a small number of images in the training set [6].

To make the final decision on the class of the analyzed image, the SoftMax layer was used with the number of outputs corresponding to the number of classes considered. The resultant class was the one that corresponded to the output of the SNA with the maximum response. One of the possible ways to take into account possible unknown classes and empty background images is to introduce a response threshold on the output layer of the SNA and treat the case "maximum response <threshold" as "not recognized".

A feature of the ResNet architecture is that the convolutional layers have 3x3 filters, as well as the fact that a quick connection is added to the network, which turns the network into its residual version.

The main point of this approach is to add paths to bypass groups of neural network layers, forming a residual block.

Deep learning-based algorithms provide a powerful framework for automatic feature generation and image classification using magnetic resonance imaging (MRI) on liver fibrosis. Such algorithms eliminate the need for manual segmentation and feature extraction from the images. However, they demand the use of a large training dataset.

Based on transfer learning being a variant of the typical deep learning-based algorithms – in that the neural network is pre-trained by a very large number of training datasets worldwide using weakly or even irrelevant image sources [7], [8] – we hypothesized that the pre-trained deep learning neural network in transfer learning approach can accurately stage liver fibrosis in a fully automated manner.

VI. DECISION SUPPORT SUBSYSTEM BASED ON FUZZY INFERENCE

Consider the conceptual framework for constructing the proposed Diagnostic Decisions Support Subsystem (DDSS) for medical. It was shown in section 2 that it receives data for processing from the following main sources of information:

- medical history;
- video;
- expert knowledge;
- printed material.

The last two of these are used for parameter system adjustment. The first two sources application is carried out in two stages. Initially, a preliminary diagnostics of the disease based on medical history. Then, depending on the results of this research, it is made a plan for further examination, in which, if it is necessary, includes MRI as one of the sections of this plan. Its results in combination with the accompanying methods of diagnostics have the greatest in formativeness in the detection of pathologies of organs.

Working with medical data involves the use of both quantitative and qualitative values. The need for this is determined by the specifics of the thinking process of the physician-diagnostician, as well as different expert opinions about the same data. In order to reduce the likelihood of misdiagnosis, it is proposed to use a modern soft mathematical apparatus to process such heterogeneous data. It includes fuzzy logic, ANN, probabilistic reasoning, and more. Probabilistic considerations relate solely to the future and lose their meaning when a random event occurs (or does not occur) at a certain point in time, so it will not be applied in the developed system. The proposed diagnostic system has the ability to evaluate the patient's current state, taking into account the analysis of his past condition, determined from the medical history. On this basis, the following components of soft calculations are used.

It is suggested to use fuzzy logic apparatus to work with qualitative data. This apparatus is a system of fuzzy inference – a system of logical inference, based on the algorithm of obtaining fuzzy conclusions based on fuzzy preconditions using the basic concepts of fuzzy logic. The fuzzy inference process combines all the basic concepts of fuzzy set theory: membership functions, linguistic variables, fuzzy logic operations, fuzzy implication methods, and fuzzy composition. Fuzzy output systems allow you to solve the problems of automatic control, data classification, pattern recognition, decision making, machine learning, and more.

Fuzzy output systems are designed to convert the values of input process variables into output variables based on the use of fuzzy production rules. For this purpose, fuzzy inference systems should include a fuzzy product policy framework and implement fuzzy inference based on the assumptions or conditions presented in the form of fuzzy linguistic statements.

Based on the above, we can conclude that these systems are widely used in medical diagnostics because they have several advantages.

1) Can process linguistic variables (LV).

2) The output algorithm is transparent for analysis, and it can be controlled simply by changing the fuzzy product rules (FPR) system.

3) It is not necessary to know the model of functioning of the object of research – it is enough only to describe it with the help of the FPR system, which will be its linguistic model.

Fuzzy product rules have different diagnostic significance. It is proposed to determine it in two stages: based on the experts' opinion, to set the initial values of the weights, and then using the apparatus of artificial neural networks to make their adjustments and change if it is necessary. As the opinions of experts are often very different, the use of ANNs in combination with fuzzy logic will allow to adjust the parameters of the diagnostic system in the best way.

The fuzzy inference system (the subsystem of decision support on Fig. 1) is presented as two functional blocks: the decision support block and the block of decision rules. This system works both at the stage of preliminary diagnostics (before the ultrasound examination) on the base of data from the medical records and together with obtaining video information.

Currently, most fuzzy inference systems are based on 6 steps:

1) formation of a base of rules of logical inference;

2) fuzzification (bringing to fuzziness) of input variables;

3) aggregation of subconditions;

4) activation of the inference;

5) accumulation of inference '

6) defuzzification (if necessary).

The main stages of fuzzy inference are presented in Fig. 4.

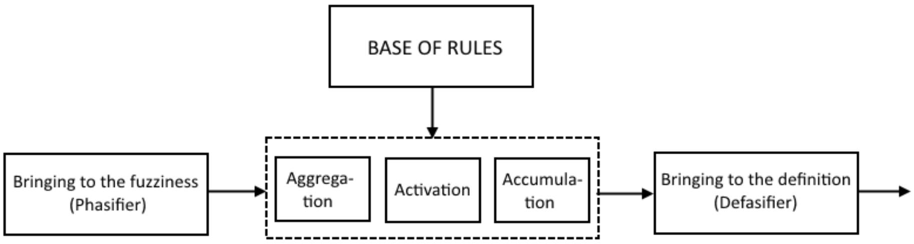

Fig. 4. The MainStagesof Fuzzy Inference

VII. CONCLUSIONS

It is considered the problem of intelligence diagnostic system construction for identification of liver fibrosis stages. As a principal technical mean it is used Magnetic Resonance Imaging. It is justified the need of Residual neural network for image processing of MRI results for identification of liver fibrosis stages due to its high accuracy of classification problem solution, taking into account the necessity of liver texture analysis. The absence of quality and enough learning sample is compensated by transfer learning approach use. The final diagnosis is formed with help of fuzzy inference system use.

Although liver biopsy is the standard of reference for diagnosis and staging of liver fibrosis, it is an invasive procedure with possible complications , so the proposal approach is less traumatic but more complicated.

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В. М. Синєглазов, М. В. Шевченко, А. Т. Кот. Інтелектуальна система діагностики стадій фіброзу печінки

Визначено необхідність побудови інтелектуальної системи діагностики стадій фіброзу печінки, для яких визначені значення параметрів що характеризують роботу печінки. В якості основного медичного обладнання, яке використовується для діагностики, розглядається магнітно-резонансна томографія. Розроблено структурну схему системи діагностики, яка включає підсистему обробки томограм і підсистема прийняття рішення. В якості базового елементу підсистеми обробки томограм використовується згорткова нейронна мережа, навчання якої проводиться за допомогою алгоритму Transfer Learning. Як параметри, що визначають стадію фіброзу печінки використовується текстура зображення. Підсистема підтримки прийняття рішення будується на основі нечекіх нейронних мереж. Наведено приклади роботи системи при визначенні стадій фіброзу.

Ключові слова: інтелектуальна система; стадії фіброзу печінки; магнітно-резонансна томографія; згорткова нейронна мережа; алгоритм Transfer Learning; текстури; нечіткі нейронні мережі.

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Освіта: Київський політехнічний інститут, Київ, Україна, (1973).
Напрям наукової діяльності: аеронавігація, управління повітряним рухом, ідентифікація складних систем, вітроенергетичні установки.
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В. М. Синеглазов, М. В. Шевченко, А. Т. Кот. Интеллектуальная система диагностики стадий фиброза печени

Определена необходимость построения интеллектуальной системы диагностики стадий фиброза печени, для которых определены значения параметров характеризующих работу печени. В качестве основного медицинского оборудования, используемого для диагностики, рассматривается магни́тно-резона́нсная томогра́фия. Разработана структурная схема системы диагностики, которая включает подсистему обработки томограмм и подсистема принятия решения. В качестве базового элемента подсистемы обработки томограмм используется сверточная нейронная сеть, обучение которой производится с помощью алгоритма Transfer Learning. В качестве параметров, определяющих стадию фиброза печени используется текстура изображения. Подсистема поддержки принятия решения строится на основе нечеких нейронных сетей. Приведены примеры работы системы при определении стадий фиброза.

Ключевые слова: интеллектуальная система; стадии фиброза печени; магнитно-резонансная томография; сверточная нейронная сеть; алгоритм Transfer Learning; текстуры; нечеткие нейронные сети.

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