Ministry of Science and Higher Education of the Russian Federation
NATIONAL RESEARCH
TOMSK STATE UNIVERSITY (NR TSU)
Faculty of Physics

ADMIT TO THE DEFENCE AT THE SEB

Director of the BEP
Doctor of Physics and Mathematics,
Professor
_____ V.P. Demkin
«15» 06 2021

MASTER'S THESIS

INVESTIGATION OF THE DYNAMICS OF THE PHYSICAL PROCESSES OF BLOOD COAGULATION BASED ON FUZZY SETS THEORY

within the Basic Educational Programme of Master's Degree «Physics Methods and Information Technologies in Biomedicine»
subject area 03.04.02 – Physics

Tsibulina Anastasiia Olegovna

Research supervisor
Doctor of Physics and Mathematics,
Professor
_____ V.P. Demkin
signature
«8» 06 2021.

PhD, Senior Researcher
_____ O.I. Zvonareva
signature
«8» 06 2021.

Author
student of group No 051963
_____ A.O. Tsibulina
signature

Tomsk – 2021

ABSTRACT

Key words: diagnostics of the blood clotting system, hemostasis system, hemostatic potential, fuzzy logic, fuzzy set theory, fuzzy neural network model.

The purpose of my research is to develop a method for assessing the human hemostatic potential using the theory of fuzzy sets to improve the diagnosis of the hemostatic system.

The object of this study is the physical processes of blood clotting. The choice of this tool is due to the scientific and practical significance of the development of methods for correcting violations of hemostatic potential.

The subject of the study is an experimental and theoretical study of changes in the hemostatic potential in various clinical situations and an assessment of the hemostatic system in conditions of incomplete and unstructured information.

The main result of our research is a method for estimating the hemostatic potential using the theory of fuzzy sets.

The developed neuro-fuzzy model has a three-layer structure: the first layer is the input features that include the patient's data (his complaints, symptoms, and other data); the second layer is represented as fuzzy rules that include the types of the hemostatic system; the third layer is the class labels (hyper-, hypo-, normocoagulation).

Testing of the neuro-fuzzy model of the blood coagulation process showed that the use of the fuzzy logic method significantly increases the reliability of determining the hemostatic potential, which has an undeniable advantage for improving the methods of diagnosing the hemostatic system. Main publications on the subject:

1. Tsibulina A. O. Mathematical model of expert information system for assessing the quality of medical technologies // Information Technologies: Materials of the 58th International Scientific Student Conference on April 10-13, 2020/ Novosibirsk State University. Novosibirsk: CPI NSU, 2020. – P. 162. (in Russian)

2. Tsibulina A. O., Kotlovskaya L. Yu., Demkin V. P., Udut V. V., Diagnostics of the state of hemostasis with the use of the theory of fuzzy sets // VII International Conference of Young Scientists: biophysicists, biotechnologists, molecular biologists and virologists-2020: Collection of tez. / ANO "Innov. TsentrKoltsovo". Novosibirsk: CPI NSU, 2020. – p. 276-277. (in Russian)

3. Tsibulina A. O. Application of a fuzzy neural network model for determining the hemostatic potential // Physical methods in natural sciences and materials science: Materials of the 59th International Scientific Student Conference on April 12-23, 2021 / Novosibirsk State University. Novosibirsk: CPI NSU, 2021. – P. 162. (in Russian)

4. Demkin V. P., Melnichuk S. V., Zavadovsky K. V., Khoryak M. N., Rudenko V. V., Suyundukova A. T., Kukartseva D. N., Tsibulina A. O., Udut V. V. Influence of dynamic blood viscosity on coronary blood flow in the stenosed section of the artery // Russian Physics Journal, 2021 (in print)

5. Demkin V. P., Udut V. V., Melnichuk S. V., Demkin O. V., Kotlovskaya L. Yu., Rudenko T. V., Tsibulina A. O., Zhukovskaya A. A. Test of thrombin generation based on the resonant-acoustic method for determining low-frequency viscoelastic properties of whole blood, 2021 (in print)

CONTENTS

LIST OF ABBREVIATIONS 4
INTRODUCTION 6
1 General understanding of the hemostatic system 8
1.1 Blood clotting system 8
1.2 Blood clotting phases 12
2 Diagnosis of hemostatic potential 14
2.1 Local (laboratory) methods 14
2.2 «Global» diagnostic methods 16
2.3 Disadvantages of hemostatic potential testing methods 25
3 Development of a method for diagnosing human hemostatic potential based on medical data 27
3.1 Neuro-fuzzy models using fuzzy set theory in medical decision support systems 27
3.2 Description of the LPTEG method 32
3.3 A physical and mathematical model for determining the coefficient of dynamic viscosity 38
3.4 Neuro-fuzzy model for HP estimation 41
3.5 Approbation of the HP estimation method using the fuzzy logic apparatus . 46
3.6 Results of testing a neuro-fuzzy model of the process for assessing the hemostatic potential 50
CONCLUSION 52
REFERENCES 57
APPENDIX A Indicators of low-frequency piezothromboelastography 63
APPENDIX B Calculated indicators of the LPTEG 64

LIST OF ABBREVIATIONS

ARP-01M "Mednord"–	diagnostic hardware and software complex for assessing the hemostatic potential of blood, acting on the basis of recording changes in the resistance of the test medium to resonant vibrations of the resonator needle
Neuro-fuzzy model –	an artificial intelligence system that combines the methods of artificial neural networks and a fuzzy logic system
ABCT –	activated blood clotting time
ADP	Adenosine diphosphoric acid
AH –	arterial hypertension
ACT –	auto-coagulation test
APTT –	activated partial thromboplastin time
AT III –	antithrombin III
ATP –	adenosine triphosphate
APTT –	activated partial thromboplastin time
BCT –	blood clotting time
HD –	hypertension
HP –	hemostatic potential
CHD –	coronary heart disease
ICC –	intensity of the contact phase of coagulation
ICD –	intensity of the coagulation drive
ICS–	information computer system
IPC –	the intensity of polymerization of the clot
ICRL –	intensity of clot retraction and lysis
ITDC –	the intensity of total blood clotting
TPI –	thrombogenic potential index
CTAA –	coefficient of total anticoagulation activity
CTA –	constant of thrombin activity
MD –	characteristic of the maximum density of the clot

LPTEG – low-frequency piezothromboelastography

RASB – the system of regulation of the aggregate state of blood

SFMC – soluble fibrin-monomer complexes

TEG – thromboelastography

GP – gelling point

TT – thrombin time

TFPI – tissue factor pathway inhibitor

INTRODUCTION

In the modern world, one of the causes of death and disability, especially in diseases of the cardiovascular system, is thrombosis, or hemorrhagic complications [1]. There are a lot of studies in the world related to the solution of the issues of diagnostics of the state of hemostasis, but this problem requires a long study, since the mechanisms of hemostasis are a complex cascade of physico-chemical reactions and research is carried out in conditions of incomplete and inaccurate information [2, 3].

In medicine, researchers have long believed that the functioning of the hemostatic system, can be evaluated solely by the results of laboratory tests, assuming that the coagulation properties correctly reflect the state of the system as a whole, in any part of the blood flow. New knowledge about the system of regulation of the aggregate state of blood (RASB) leads to the addition of existing methods, as new research on the physical mechanisms of changes in the rheological properties of blood appears.

In laboratory diagnostics, there is a whole range of different methods, which gives the impression of a complete and comprehensive assessment of the hemostatic potential [4-9]. Unfortunately, most of the methods used have a number of disadvantages, such as low sensitivity of tests, problems of the preanalytic stage, problems of assessing coagulation in real time, etc. Conducting research using existing methods excludes a holistic view of the hemostatic system, since the information obtained is fragmented and unstructured. Very often, similar symptoms, test results, and other factors may overlap, indicating different diseases, thereby creating the problem of making the right decision from different alternatives.

Thus, the fuzzy nature of the boundaries between similar diseases makes it impossible to build a correct classical mathematical model and requires the development of new methods that allow processing fuzzy and incomplete information. These methods should be studied using fuzzy set theory.

In order to achieve this goal, our study used one of the most optimal global

tests – a method of low-frequency piezothromboelastography [10-12]. This method allows us to assess the state of the hemostatic potential (HP) by measuring the dynamics of the viscoelastic characteristics of whole blood at all stages of the process of its coagulation: from the "damage" of the vascular wall of the vein during blood sampling to the formation of a fibrin-platelet clot. The use of the LPTEG method makes it possible to see changes in the characteristics of blood and allows you to control HP.

The purpose of my research is to develop a method for assessing the human hemostatic potential using the theory of fuzzy sets to improve the diagnosis of the hemostatic system.

In order to perform the study, we set the following tasks:

1. Conducting experiments to study the hemostatic system in various clinical settings using the method of low-frequency piezothromboelastography.

2. Selection and study of key factors affecting hemostatic potential disorders.

3. Development of a neuro-fuzzy model for determining hemostatic potential disorders using data obtained by low-frequency piezothromboelastography.

4. Approbation of the method for assessing the potential of hemostasis based on the created neuro-fuzzy model in various clinical situations (coronary heart disease, hemophilia, healthy people).

1 General understanding of the hemostatic system

1.1 Blood clotting system

The hemostasis system is a biological system that provides rapid and effective prevention and stopping of bleeding, maintaining a sufficient volume of circulating blood in the bloodstream and thereby ensuring normal blood supply to the organs [13].

Key participants in the process:

– structural components of the vessel walls (endothelium);

– blood cells (platelets);

– plasma enzymes (coagulation, anticoagulation, plasmin and kallikrein-kinin systems.

The hemostatic system promotes a clear interaction of the mechanisms of positive and negative communication. Initially, the hemostasis is self-activated, and due to the increase in the anti-clotting potential, self-rejection occurs. In this process, only a small part of the coagulation factors becomes active.

There are two types of hemostasis:

– primary (vascular-platelet hemostasis), which contributes to the formation of a white platelet thrombus;

– secondary (coagulation) hemostasis occurs with the participation of blood clotting factors and provides the formation of a fibrin thrombus.

Primary (vascular-platelet hemostasis)

Primary hemostasis begins with a spasm of blood vessels and ends with the appearance of a plug of platelets, which formed within 1-3 minutes.

Primary hemostasis has the following processes:

– spasm of the damaged vessel;

– gluing (adhesion) of platelets at the site of injury;

– platelet crowding;

– irreversible adhesion of platelets;

– formation of a platelet clot.

1. Spasm of damaged blood vessels.

The spasm occurs reflexively in the first seconds after the damage to the vessel. There will be no bleeding at this point. This occurs because the cells of the vessel walls contract under the influence of norepinephrine, released from the damaged vessel, and catecholamine, the concentration of which increases due to stress.

2. Platelet adhesion to the site of injury

Platelet binding occurs because the injury site becomes positively charged, and platelets have a negative charge. With the participation of receptors, they attach to the Willebrand factor and collagen in the damaged area.

3. Accumulation of platelets at the site of injury

The adhesion of platelets to the damaged vessel leads to the formation of their aggregates. The activators of this process are ADP, ATP, Ca++, and thromboplastin. As a result, a loose plug is formed, which is reversible.

4. Irreversible platelet aggregation

Platelets begin to form a dense plug that prevents the penetration of plasma. This process is affected by thrombin. Thrombin releases calcium ions, and irreversible aggregation is initiated, which promotes the breakdown of platelets and the release of biologically active substances.

Platelets begin to form a dense plug that prevents the penetration of plasma. Thrombin affects this process. Thrombin releases calcium ions, and irreversible aggregation is initiated, which will lead to the breakdown of platelets and the release of biologically active substances.

Thromboplastin, which begins to be released, triggers secondary hemostasis and the formation of a small number of fibrin filaments occurs.

5. *Platelet thrombus retraction*

There is a reduction in the clot and the platelet plug is compacted. Fibrin filaments seal the blood clot. Factor (F9) stabilizes the blood clot. This causes the bleeding to stop.

In small vessels, bleeding stops mainly due to primary hemostasis. In large vessels, due to high pressure, the formation of a blood clot occurs as a result of secondary hemostasis.

Coagulation (secondary) hemostasis

Secondary hemostasis involves a dense blockage of the damaged vessel with a blood clot. This hemostasis is involved in stopping bleeding due to the formation of fibrin clots.

The main factors involved in blood clotting:

– plasma clotting factors;

– blood clotting factors of shaped blood elements;

– tissue clotting factors.

Plasma factors are of the greatest importance:

I. *Fibrinogen* is a globular protein that synthesized in the liver. Under the influence of thrombin, it turns into fibrin. Forms the fibrillar network of a blood clot. Stimulates tissue regeneration.

II. *Prothrombin* is a glycoprotein. Under the influence of prothrombinase, it turns into thrombin, which has proteolytic activity in relation to fibrinogen.

III. *Thromboplastin* consists of apoprotein III protein and phospholipids. It is a part of the membranes of blood cells and tissues. It is the matrix where prothrombinase formation reactions take place.

IV. *The ions* Ca^{2+} are involved in the formation of complexes that are part of prothrombinase. They stimulate clot retraction, platelet aggregation, bind heparin, and inhibit fibrinolysis.

V. *Proaccelerin* is a protein that is necessary for the formation of thrombin. Binds X-factor to thrombin.

VI. Excluded from the classification.

VII. *Proconvertin* is a glycoprotein. It is necessary for the formation of prothrombinase.

VIII. *Antihemophilic globulin A forms a complex molecule with the Willebrand factor. Required for the interaction of IXa with X. In its absence, hemophilia A develops.*

Willebrand factor (FW) is formed by the vascular endothelium and is necessary for platelet adhesion and stabilization of factor VIII.

IX. *Christmas factor*-antihemophilic globulin B. Glycoprotein. Activates the X factor. In its absence, hemophilia B develops.

X. *The Stewart-Prauer factor* is a glycoprotein. Ha is a part of prothrombinase. Activated by factors VIIa and IXa. Converts prothrombin to thrombin.

XI. *The plasma precursor of thromboplastin* is a glycoprotein. It is activated by factor Xiia, kallikrein, high-molecular kininogen.

XII. *Hageman factor-protein. It is formed by the endothelium, white blood cells, and macrophages. Activated by contact with a foreign surface, epinephrine, kallikrein. It starts the process of prothrombinase formation, activates fibrinolysis, and activates factor XI.*

XIII. *Fibrin-stabilizing factor (FSF)* – fibrinase. It is synthesized by fibroblasts, megakaryocytes. Stabilizes fibrin, activates regeneration.

Fletcher's factor activates factor XII, a plasminogen.

The Fitzgerald factor is a high-molecular-weight kininogen. It is formed in the tissues, activated by kallikrein. Activates factors XII, XI, fibrinolysis [14]

An important role of the coagulation system is to stop bleeding by blocking the vessel with a red blood clot, which includes fibrin fibers and elements of red blood cells and platelets.

Also involved in blood clotting are tissue and cellular factors and calcium ions.

1.2 Blood clotting phases

Blood clotting is a chain process of transition from the soluble protein fibrinogen to the insoluble fibrin. In the process of hemocoagulation, there is a consistent work of activated blood clotting factors.

Hemocoagulation has three phases:

1) formation of prothrombinase;

2) formation of thrombin (from inactive prothrombin under the influence of prothrombinase);

3) formation of fibrin (from fibrinogen under the influence of thrombin) [15-17].

The first phase (formation of prothrombinase) is the process that can convert prothrombin into thrombin. This phase lasts 5-7 minutes.

The first phase has an external and internal pathway of prothrombinase formation. *The external mechanism* looks like this: due to the injury, the cells are damaged and the tissue thromboplastin (F3) is released, and this process takes 5-10 minutes. In addition to thromboplastin, convertin (F7) and calcium ions are involved. This complex promotes the formation of the first portions of fibrin from fibrinogen and this process occurs within 5 seconds after damage.

The start of the internal mechanism also occurs due to damage to the vessel, but here the platelets rush to the site of damage, there the plasma factors, for example, F12 (Hageman factor), are activated. When factor 12 is in contact with collagen, the factor is activated and then there is a cascade process of activation of factors XI, IX, VIII with the participation of calcium ions (IV). A complex of these factors activates the X factor, thereby forming the right amount of prothrombinase. This process takes 5-10 minutes (Figure 1).

The second phase (formation of thrombin) occurs with the participation of prothrombin (FII), which in the presence of calcium ions and under the influence of prothrombinase (FXa) turns into thrombin (F.IIa). The duration of the phase is 2-5 seconds.

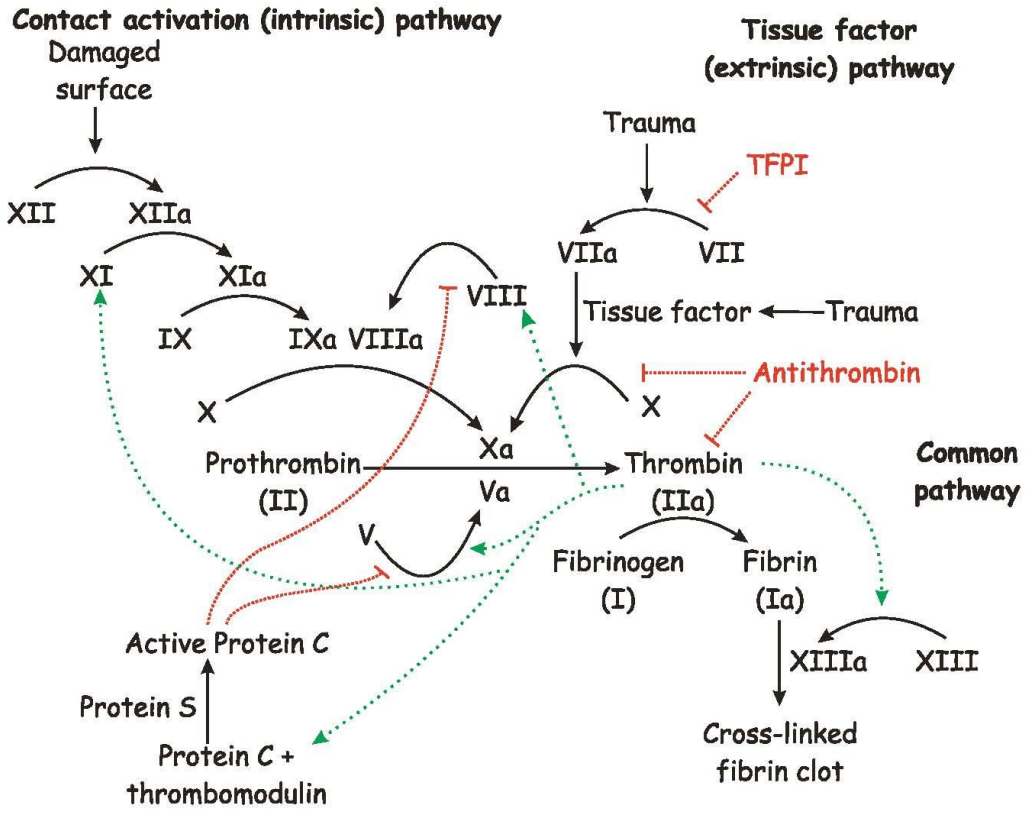


Figure 1 – Cascade model of coagulation

The third phase (formation of fibrin)

Thrombin, cleaves peptides from the fibrinogen molecule converts fibrinogen (F.I) to fibrin (F.Ia). First, a fibrin monomer is formed, then a soluble fibrin polymer. Factor XIII (fibrin-stabilizing) strengthens the fibrin-polymer bonds and converts soluble fibrin to insoluble.

Next, the clot is retracted with the help of platelet contractile protein (thrombostenin) and calcium ions with the active contraction of fibrin fibers. Due to retraction, the clot becomes more dense, a full-fledged blood clot is formed, which ensures the final stop of bleeding.

Thus, vascular-platelet hemostasis is a temporary stop of bleeding. Coagulation hemostasis is the final stop of bleeding with the help of a fibrin clot. This process takes place in three stages. The first stage can take place on the external and internal path, and then on a single path. The final product of clotting is fibrin.

2 Diagnosis of hemostatic potential

2.1 Local (laboratory) methods

In modern diagnostics, there is a large selection of methods and technologies that are used to study the hemostatic potential.

From laboratory methods it is necessary to distinguish:

1. Measurement of platelet count and measurement of platelet activity.

2. Clotting tests, which examine the activity of hemocoagulation factors. In these tests, the formation of a fibrin clot is a unit of measurement.

3. Enzyme immunoassay methods. These methods help to determine the concentration of the test factor when using monoclonal antibodies [18].

There are also genetic methods that can detect mutations in genes associated with blood clotting factors and fibrinolysis.

The first group of laboratory methods includes screening tests.

These include:

1. Estimation of platelet count;

2. Determination of bleeding time;

3. Prothrombin time;

4. Activated partial thromboplastin time;

5. Determination of the level of fibrinogen;

6. D-dimer.

These tests are included in the primary research link.

The second group includes additional tests to detect various disorders of hemocoagulation:

1. Bleeding (a study of the bleeding time, counting the number of platelets and their adhesion, determining the activity of the Willebrand factor, prothrombin time, determining fibrinogen and the activity of factors VIII or IX and etc.).

2. Conducting venous or arterial thrombosis (counting the number of platelets, determining the activity of antithrombin, the presence of genetic mutations, determining the D-dimer, etc.).

3. Intravascular coagulation (necessary for the diagnosis of DIC-syndrome).

4. Anticoagulant therapy.

Brief description of assessment tests

1. APTT-activated partial thromboplastin time

The principle of the method involves determining the clotting time of the decalcified plasma after the addition of the calcium mixture. This mixture activates factors XII, V, and VIII, which contributes to the evaluation of fibrin formation.

Doctors conduct a study conducted using a coagulometer.

An important requirement is the use of stable reagents that are adapted for specific tasks.

2. Prothrombin time

The principle of this method is to determine the time of formation of a fibrin clot after the addition of a calcium mixture. This mixture activates factor VII and ensures the functioning of the external cascade of fibrin formation. The prothrombin test is used to assess the state of the hemocoagulation system. Calibration of the method for determining the International Normalized Ratio (INR) in capillary blood is too time-consuming for a conventional clinical diagnostic laboratory. It is important that the reagents are calibrated by their manufacturer.

3. Determination of fibrinogen

The most common method for determining fibrinogen by Clauss. The principle consists in the interaction of diluted plasma fibrinogen with high-concentration thrombin. The reaction time of clot formation depends on the amount of fibrinogen.

4. Thrombin time

The principle of the test is the interaction of thrombin with fibrinogen (the final stage of clotting). Thus, the lengthening of the thrombin time is a consequence of a decrease in the amount of fibrinogen in the plasma, a violation of the structure of fibrinogen, etc.

It would seem that the set of the above methods is impressive, but, unfortunately, in practice, due to the high cost, a rather limited set of tests is used, for example, APTT, PV, fibrinogen, D-dimers [19-21].

The results of local methods can only give an approximate description of the hemostatic potential and, unfortunately, the fragmentary and incomplete understanding of the hemostatic system is still a big problem in medical practice.

2.2 «Global» diagnostic methods

The main diagnostic methods usually include the thrombin generation test, thromboelastography(TEG), low-frequency piezothromboelastography (LPTEG) and thrombodynamics [21-22].

1. Thrombin generation test

In 1953, researchers first used this test to assess hemostasis in patients with hemophilia. The principle of the test is to determine the amount of thrombin formed during the recalcification of citrate blood plasma in the presence of a fixed concentration of tissue factor and a fluorogenic substrate.

Over a certain period of time, using a fluorometer and computer processing, the area of the thrombin generation curve is measured, which has an ascending part, a section of reaching the maximum and a descending part that shows the inactivation of the enzyme [23, 24].

This test belongs to the global assessment methods and allows you to evaluate hemostasis in general (Figure 2).

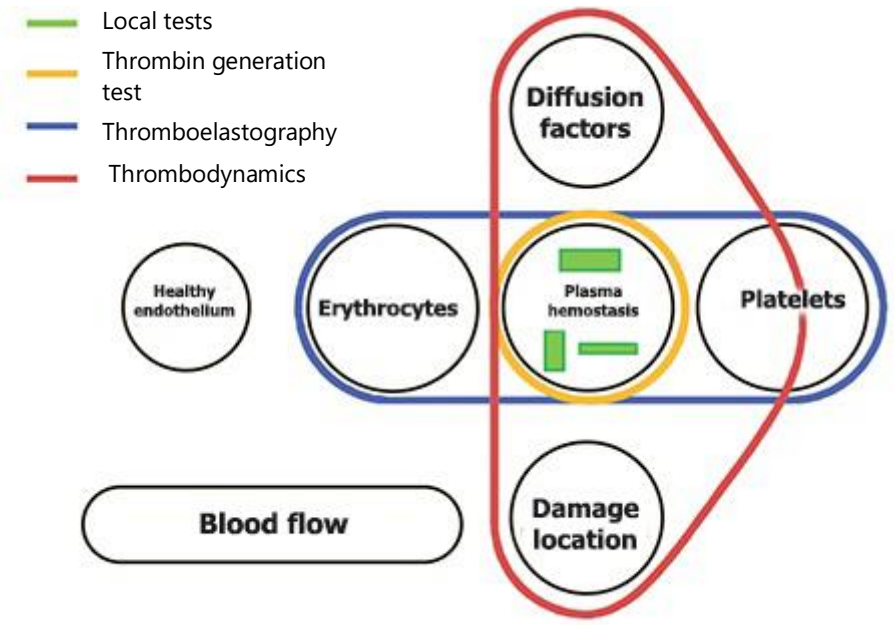


Figure 2 – Global tests for assessing hemostasis

Currently, doctors test the generation of thrombin with the help of fluorimeters or automatic analyzers. The technique with the help of a fluorometer is that in the well of the tablet we must put a mixture of plasma mixed with an activator (the activator is the human factor and phospholipids with a negative charge).

At a temperature of 37 degrees, the mixture will be incubated, and to start blood clotting, a buffer containing ionized calcium is added to the wells. Thrombin begins to break down the substrate, resulting in the formation of fluorophosphorus molecules. This radiation is recorded at the same time intervals. The more intense the glow, the higher the concentration of thrombin. These measurements contribute to the construction of the thrombin generation curve (Figure 3).

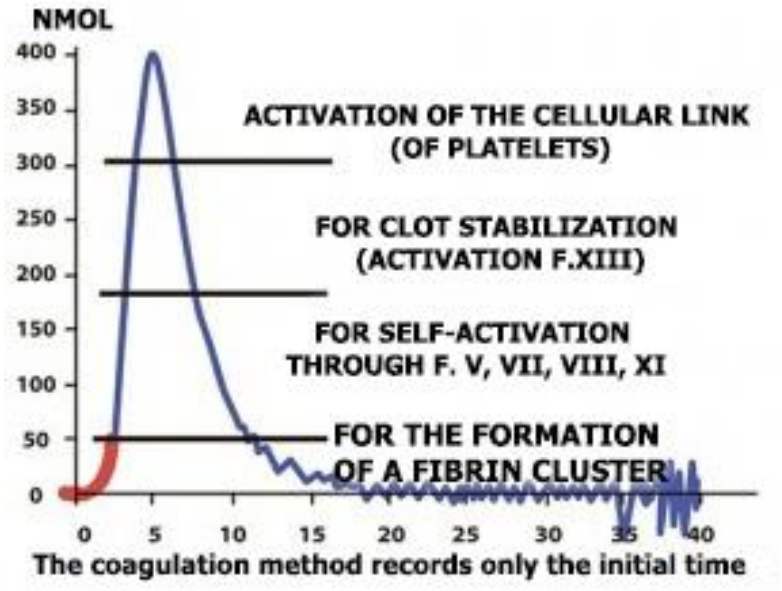


Figure 3 – The curve of the thrombin generation test

The curve of the TGT has the following indicators:

– lag time – the time from the beginning of applying a mixture of fluorogenic substrate and ionized calcium to the well with the sample and activator until the signal deviates from the horizontal line by more than 2 standard deviations.

– peak thrombin, nmol/L - this is the point where the maximum concentration of thrombin occurs, during the generation process in the sample;

– time to peak, min – the time it takes to reach the maximum concentration of thrombin in the sample;

– endogenous thrombin potential – the area under the thrombin generation curve (Figure 4).

Thrombophilia and hemophilia are well diagnosed using the thrombin generation method.

The peculiarities of using the thrombin generation test are that the coagulogram indicators may be within the normal range, while the TGT will reveal an increase in some parameters, which will indicate coagulation.

Thus, TGT is a global method for assessing the hemostatic potential. It used to diagnose thrombophilia, hemophilia, monitor therapy and control the effectiveness of coagulants, control DIC syndrome.

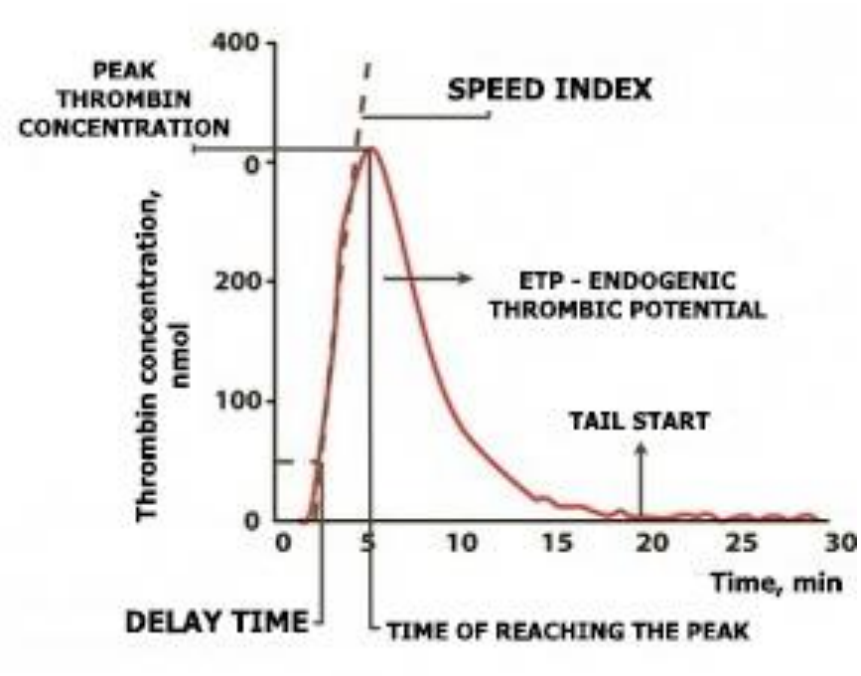


Figure 4 –The main indicators of the thrombin generation test

2. Thrombodynamics

This test evaluates the spatiotemporal dynamics of blood clotting. The test is performed under conditions similar to in vivo clotting conditions. When performing thrombodynamics, the blood plasma is placed in a measuring cuvette located in a water thermostat. A special activator introduced into the cuvette channel, on which a nanocoating with a tissue factor is applied. A video camera captures the process of forming a fibrin clot. The information on the frames shows the process of blood clotting in detail (Figure 5).

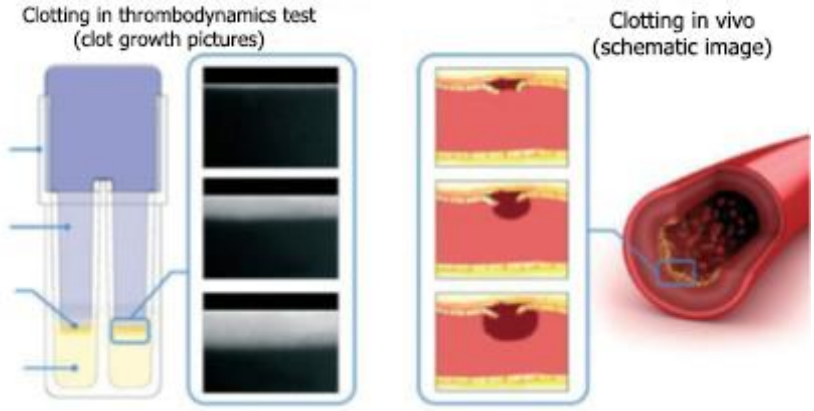


Figure 5 – The principle of measuring thrombodynamics

Basic parameters of thrombodynamics:

– tlag (min) – the time from the moment of contact of the blood plasma with the activating surface and until the beginning of clot growth;

– C_s – clot size after 30 minutes;

– V (mkm/min) – clot growth rate (central phase);

– V_i (mkm/min) – initial growth rate of the clot;

– Tsp (min) – time of occurrence of spontaneous clots in the plasma volume;

– D – the density and size of the clot, which characterize the structure of the fibrin clot, the concentration of fibrinogen in the blood plasma and the growth of the clot [25].

The study of the hemostatic system using the method of thrombodynamics makes it possible to obtain information about the presence of thrombosis or bleeding, and assesses the effectiveness of anticoagulant therapy.

3. Thromboelastography (TEG)

This method provides a reliable estimate of the clot when using a small amount of whole blood, and it also helps in assessing the increase in blood viscosity as a clot forms and simultaneously recording this process.

Citrate blood needed for the test. The principle of the method involves incubating 360 µl of whole blood in a heated cylindrical cuvette. This cuvette oscillates for 10s at an angle of 4°45’ in a bowl with a pin loosely suspended and connected to a wire [26].

To estimate the parameters calculated on the basis of the data obtained, it is customary to estimate the time of formation and lysis of the clot. The converter records the entire process graphically [27].

There are different ways to measure viscoelastic parameters, for example, the principle of operation of a classical TEG involves rotational vibrations of a cuvette with a blood sample relative to the sensor (Figure 6)

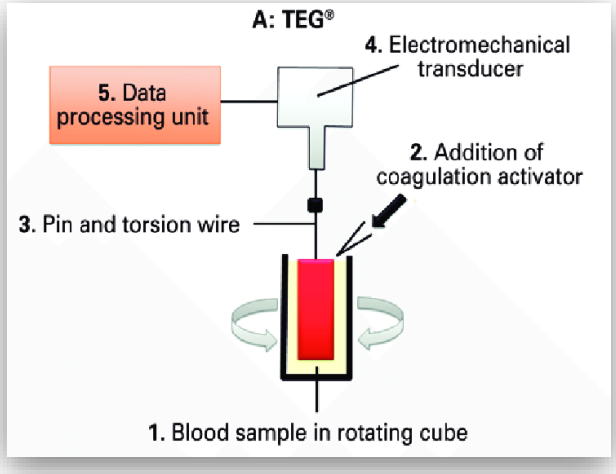


Figure 6 – The principle of operation of classical thromboelastography

A thromboelastogram is the result of registering the process and it displays the process of clot formation (Figure 7)

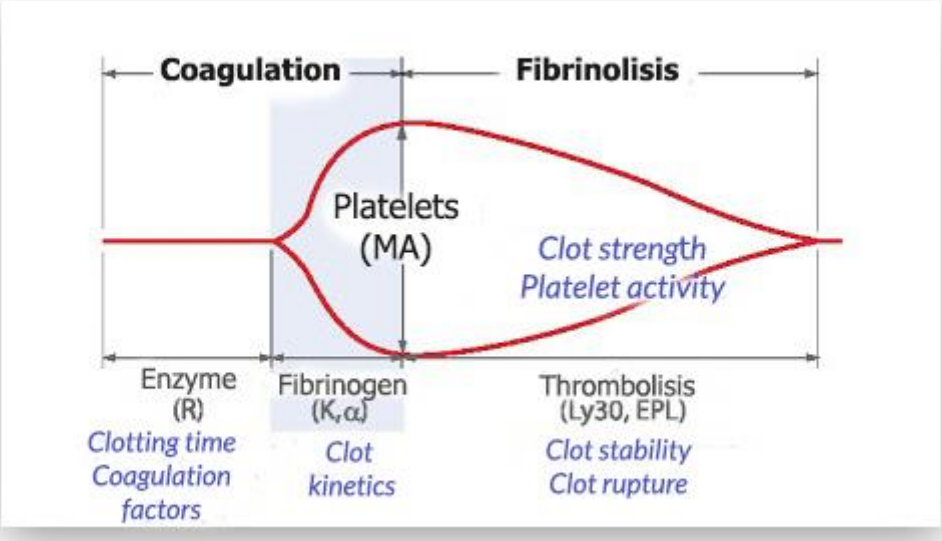


Figure 7 – Thromboelastogram of the TEG5000 device

The main disadvantages of the method should also include the problems of standardization, also this device is not made in our country and has a high cost. In addition, it should be noted the different spectrum of data on different devices and

the insufficient sensitivity of the method in assessing the hemostatic system in the case of hypoxia and hypotheremia [26, 27].

4. Low-frequency piezothromboelastography (LPTEG)

The development of methods of thromboelastography led to the appearance of a test based on vibration viscometry. This technology works with the help of the ARP-01 «Mednord» analyzer. This method helps to evaluate the pharmacodynamics of antithrombotic drugs [28-30].

LPTEG helps in the study of the whole blood hemocoagulation process, the assessment of the viscoelastic properties of the clot.

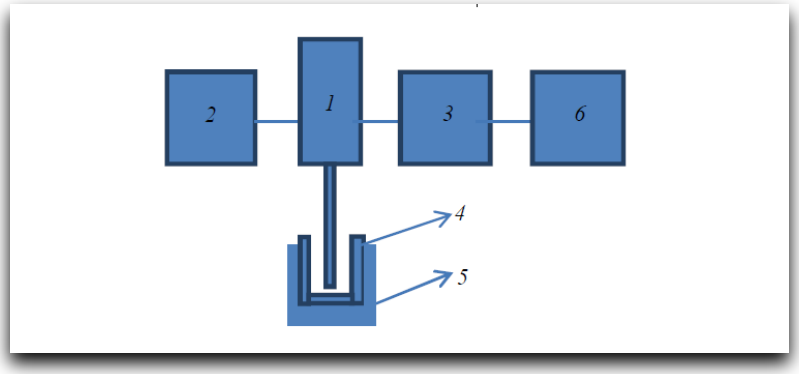
The principle of operation of low-frequency thromboelastography consists of recording changes in blood resistance using a resonant oscillation of a resonator needle. We need to fix this needle on a piezoelectric element and lower it into the blood cell [28, 31].

Previously, we need to adjust the frequency of needle vibrations in the air and in the liquid automatically, until there is no difference between the amplitudes of needle vibrations in the air and in the blood.

The measuring circuit of the device Controls the electromechanical part and with the help of the computer program «X GEMO-3», all calculations, graphs and parameters are output.

The measuring element of this device is a piezoelectric sensor. On the one hand, this sensor converts the input voltage of a low-frequency harmonic signal into mechanical vibrations that go to the test body. On the other hand, the sensor converts mechanical vibrations into the voltage of the output signal, it is already transmitted through the output amplifier to the computer, where it is processed using the "X GEMO-3" system.

Figure 8 shows the scheme of low-frequency thromboelastography [28].



1 – piezoelectric sensor; 2 – pulse generator;

3 – output operational amplifier; 4 – measuring cell;

5 – the thermostat; 6 – information and computer system "X GEMO-3"

Figure 8 – Structural and measuring scheme of the device

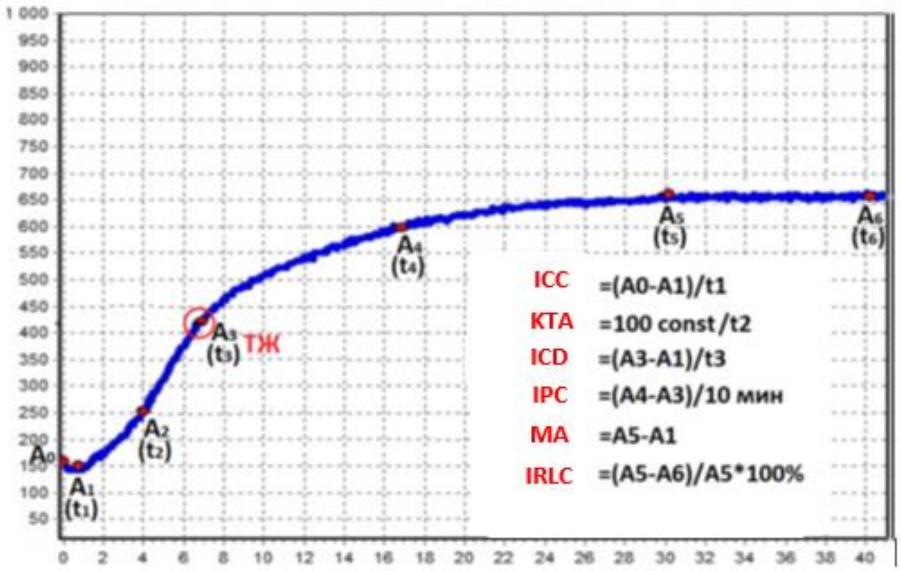
Before using the nm device, it is necessary to draw blood from the patient's vein using a silicone syringe with a rubber cuff of one volume (1 ml) without applying a tourniquet.

After taking the blood, it should be placed for 10 seconds in a measuring cuvette.

The basis for the analysis of the LPTEG image is the changes in the relative values of the viscoelastic properties of blood (Ai) occurring during coagulation, from blood collection to reaching the maximum density of the clot in the process of polymerization and retraction.

The transition of blood from the liquid state to the solid-elastic state is determined in the form of the LPTEG curve. Each point of the curve (F_i) shows the state of the system at a particular time (T_i).

The change in the aggregate state of the blood of a healthy person is shown in Figure 9.



A_0 – A_5 – the amplitude showing the formation of fibrin;

A_6 – amplitude at the 10th minute of clot lysis;

t_3 – gelling point; MD – maximum density of the clot.

Figure 9 – Diagram showing the amplitude of low-frequency piezothromboelastograp

The ordinate axis represents the amplitude of the process under study (A_1) in relative units, and the abscissa axis represents the study time (t_1) in minutes.

Figure 10 shows a graph of changes in the aggregate state of the blood (the recorded indicators of the LPTEG are indicated in Appendix A, the calculated indicators are indicated in Appendix B)

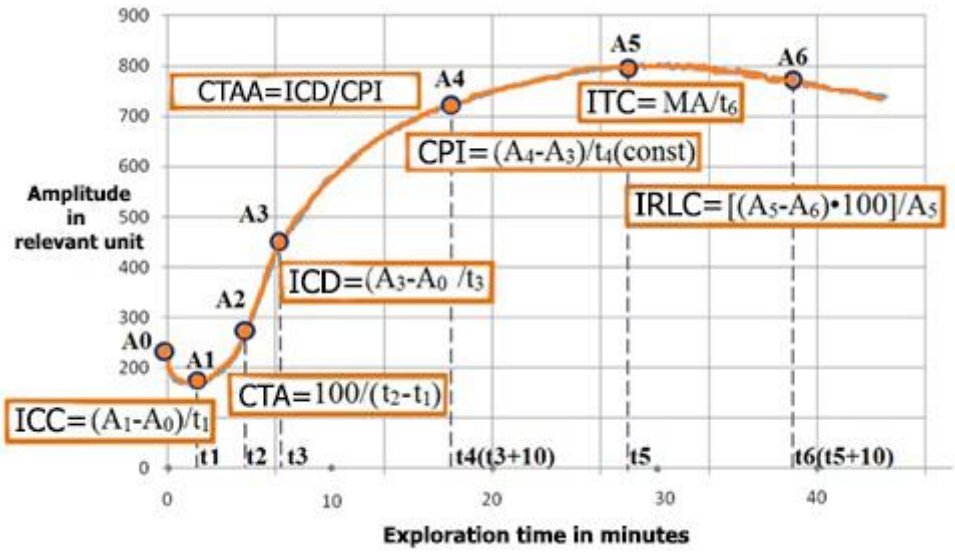


Figure 10 – Indicators of changes in the aggregate state of blood (LPTEG)

Low-frequency piezothromboelastography is currently one of the best global tests that allows the assessment of all stages of fibrinogenesis, from initiation to fibrin formation [19].

The assessment of the recorded signals when assessing the hemostatic potential is based on the analysis of three basic indicators: hypocoagulation, hypercoagulation and normocoagulation (Figure 11).

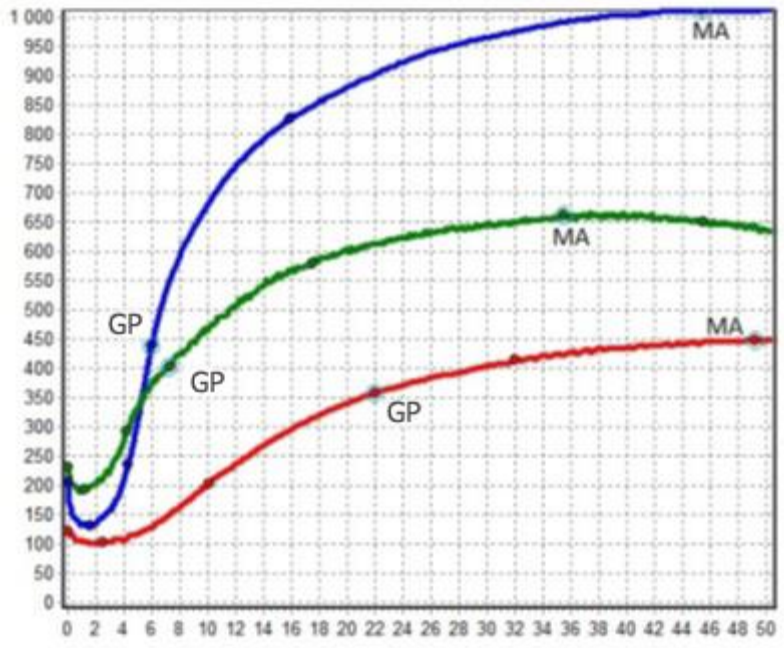


Figure 11 – Displacement of the LPTEG curves at the normo- (----),hypo - (----)and hypercoagulable (----) state

2.3 Disadvantages of hemostatic potential testing methods

Disorders of the hemostatic system in various patients are complex, since in addition to the disease itself, many factors affect the diagnosis, such as the therapy used, any concomitant diseases, etc.

In the study of hemostasis, there are certain principles: first, at the beginning of the study, specialists use local methods for assessing hemostasis (bleeding time, APTT, thrombin time, fibrinogenesis concentration, D-dimer will be determined).

If a more detailed study is required, then the next stage will be carried out clarifying studies, such as the study of platelet aggregation with various inducers (adenosine diphosphate, collagen, ristomycin), the activity of the Willebrand factor, the activity of factors of the coagulation, anticoagulation and fibrinolytic systems, the detection of lupus anticoagulant and many other tests [19].

The informativeness of any research method depends on the correct compliance with the preanalytic stage. Very often, rapid blood collection can lead to foaming, which, in turn, leads to the fact that the platelets go into an active state. If the blood intake is too slow, then there is an excessive activation of fibrinolysis and at the same time, an irreversible activation of clotting [21].

In order to resolve the issue of the preanalytic stage, the blood must be stored for a short time and must be taken according to special rules. Unfortunately, even the correct blood collection is able to diagnose, is able to give too limited information. Quite often, local tests are insensitive to hyper- or hypocoagulation, and these methods do not allow us to evaluate the hemostasis system in real time.

Quite often, laboratory diagnostics is faced with the problem of interpreting tests of the same name with reagents from different companies, since there is no standardization of the results. In addition, activators use high concentrations of substances that exceed the actual concentrations in the human body.

Unfortunately, standard methods for assessing the hemostatic potential, despite the large selection, make it difficult to prevent thrombohemorrhagic complications in a timely manner. Local tests mainly assess the concentration of individual proteins and are able to indicate the functioning of individual components of the hemostatic system.

This suggests that local methods are not able to assess the balance between procoagulants and anticoagulants. The emergence of new methods for assessing hemostasis shows that the standard test panel needs to be supplemented and expanded with new informative ways that will contribute to the correct diagnosis.

Thus, we should highlight the shortcomings for evaluating the hemostatic system:

– the informativeness of any test depends on the correctness of the preanalytic stage;

– the tests are not sensitive to the phenomena of hypercoagulation and hypocoagulation;

– it is not possible to evaluate the coagulation process for a particular person in real time;

– problems of standardization of test results [9];

– inaccuracy or fragmentary nature of the analyses obtained.

Also, the main, generally accepted disadvantage is the problem of long-term sample preparation (stabilization of whole blood, separation of blood into components, recalcification).

Due to the large number of shortcomings of HP assessment methods, special interest was directed to the development and implementation of new methods for diagnosing the hemostatic system, which complements existing tests.

3 Development of a method for diagnosing human hemostatic potential based on medical data

3.1 Neuro-fuzzy models using fuzzy set theory in medical decision support systems

In 1965, Lotfi Zadeh first proposed the concept of a fuzzy set [33].

There are basic concepts on which the theory of fuzzy sets is based:

1. The knowledge and skills used by a person are not perfect.
2. Knowledge may be questionable or untested.
3. The solution to the problem often consists of approximate initial data.
4. The more complex the system, the more complex its modeling is, so it is easier to model the behavior of the control system than to model the system itself.
5. Instead of using precise mathematical calculations, it is more efficient to use qualitative assessments of the situation and apply certain processing measures. [34-36].

It is known that in classical set theory, elements either belong to a set or do not belong, and the concept of a fuzzy set can assume a partial membership in the set, i.e. each element belongs to the set slightly or partially. Accordingly, the outline of the fuzzy set will have «blurred» boundaries (Figure 12) [35]

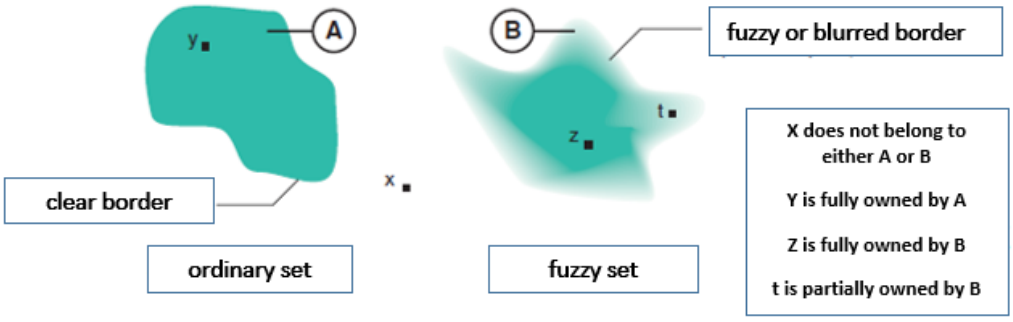


Figure 12 – Comparison of ordinary and fuzzy logic

The theory of fuzzy sets allowed us to expand the boundaries of classical set theory. Classical mathematical logic works only with strictly formalized data, and the ownership of an object is determined only by two concepts: "the object belongs to a particular set" or "the object does not belong to a particular set". Lotfi Zadeh removed the concept of "belonging" and introduces the concept of "degree of belonging", and instead of" sets " – "fuzzy sets".

In medical practice, one of the most difficult problems is the problem of the uncertainty of the choice of medical information. The problem of choosing the right solution is associated with the lack of conditions for completeness of information, medical errors, due to the inconsistency of the knowledge base.

When we model any tasks in medicine, there are almost always no true-false statements, since there are no clear boundaries in medicine. Any concept in medicine has no clear boundaries, such definitions as "severe pain", "high temperature", etc., indicate that even the truth of the statement itself is unclear.

The problem of a clear choice of alternative criteria very often makes it impossible to build a strict mathematical model of the chosen problem and the only way out is to use expert assessments when making decisions. To solve the issues of

uncertainty in medical decision support systems, it is necessary to apply the theory of fuzzy sets developed by Latfe Zadeh, on the basis of this theory, fuzzy logic is built [363738].

The introduction of fuzzy sets, namely classes with inaccurately defined boundaries that describe membership functions, contributes to the development of a more flexible approach necessary for modeling complex systems. Their behavior is described by linguistic variables that are expressed in words from a natural or artificial language.

Set A = $\{a_1,a_2 \ldots a_n\}$ – is a universal set consisting of an arbitrary set of data. In this case, the fuzzy set S =$\{\mu_s(a_i), a_i\}$, and ∈ A specifies the degree to which $\mu_s(a_i)$ belongs to the set A of the object ai defined on the set A.

Function $\mu_s(a)$ – a membership function whose range of values is a unit interval [0;1]. If $\mu_s(a)$ equal to 0, then the object a - does not belong to the fuzzy set Aβ. If $\mu_s(a)$ equal 1, then the object a-absolutely belongs to the fuzzy set A. Thus, the higher the values of μs (a), the higher the degree of belonging to the fuzzy set A. When modeling fuzzy models, knowledge is represented using concepts such as linguistic variable and fuzzy variable [36, 39, 40].

A fuzzy variable is characterized by a triple (α, Q, P), where α – name of the fuzzy variable, Q = $\{q_1, q_2, q_3 \ldots q_n\}$ - *a* universal set consisting in the domain of the definition of a fuzzy variable α; $P = \{\mu_P(q_I), q_I\}$, where $q_I \in Q$ - fuzzy set on *a* set Q, which describes the constraints $\mu_P(q_I)$, on the values of a fuzzy variable α.

A linguistic variable is a variable that defines a set of words that characterize certain properties. In medicine, it is a set of five variables (β, T, Q, G, M), where β – name, T – the set of its values (term-set), Q – scope of definition; G – a procedure that allows you to perform operations with a term set T, M – a procedure by which each new linguistic variable can be transformed into a fuzzy set.

For example, the linguistic variable "body temperature", "pressure", "cough" , etc., and the term-sets to them ("high", "low"," weak"," frequent"," happens", "does not happen". Each term-set element of a linguistic variable represents a fuzzy variable.

Models using the fuzzy logic method in medical decision support systems allow you to obtain new knowledge based on existing ones using logical inference using fuzzy logic. These systems include a set of fuzzy rules of the form:

IF "premise", then "conclusion".

When building rules, 3 types of fuzzy statements are used:

1**. *a-there is b,***

where *a* reflects a certain parameter; *b* – a name that is a fuzzy estimate.

2. ***⟨a there is α b⟩, ⟨βa there is b⟩, ⟨ βa there is α b ⟩, ⟨α a there is β b⟩,***

where ***α*** **-** modifier (it corresponds to words like: very, medium, more or less, etc.);

β **–** quantifier (for example, the use of words: a little, a lot, a lot, a few, etc.).

3. This type works by using fuzzy statements or conjunctions: AND; OR; IF...THEN.

Such fuzzy statements allow you to evaluate the truth or falsity of a certain degree of confidence, this will help to build a fuzzy conclusion.

A neuro-fuzzy model consists of a set of fuzzy rules that define a fuzzy relationship between sets of conclusions. Each element of a term set has a fuzzy set whose elements are possible values. The membership of a set is defined by the membership function whose values are located on the segment from [0; 1]. The membership function assumes the degree to which an element corresponds to a given concept.

Models based on the theory of fuzzy logic are often used in medical practice, so the disease may very well have atypical symptoms and masquerade as others. The multivariate nature of clinical manifestations makes it difficult to make diagnostic and prognostic decisions.

Diseases, their symptoms, and the results of tests may overlap with each other, which indicates that the signs are inaccurate and may affect the diagnosis and treatment. Thus, the identification of input data is carried out using fuzzy sets and the corresponding membership functions.

The general scheme of the linguistic model of the expert system is shown in Figure 13 [38, 41].

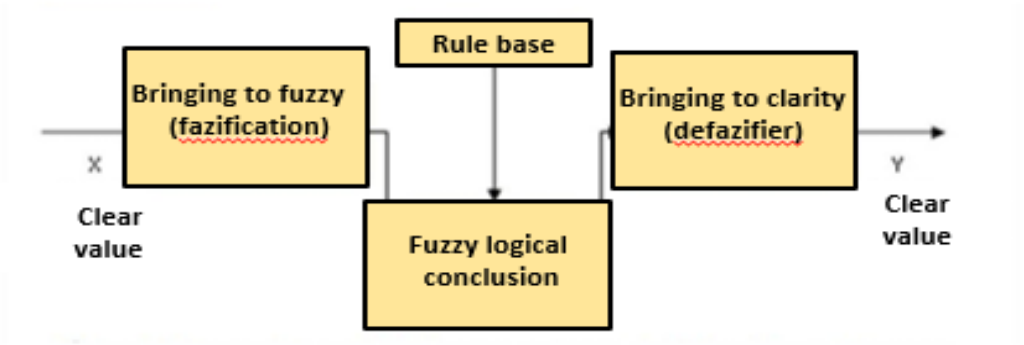


Figure 13– The scheme of the linguistic model of the expert system

Generating the output will have the following steps:

1. A selection of the set of all input data that describe the object is created.

2. The most statistically significant ones are selected from them.

3. The input data is fuzzified and a term set with an interval of changes is set for each variable.

4. A rule base is being developed that reflects a particular relationship between input and output variables.

5. Fuzzy output is performed based on the received data [44].

The most important step is to build a rule base, as this affects the effectiveness of the entire system as a whole. The inference rules are carried out by convolution of statements to obtain an integral condition corresponding to the entire set of statements in the conditional part of the rule.

The process of defuzzification involves the process of moving from the membership function to a specific numeric value. Defuzzification is performed using methods such as the maximum membership function method, the center of gravity method, the area bisector method, and the left or right modal value method.

Thus, the use of a neuro-fuzzy model in medicine can be a fairly effective method that will allow you to make correct medical decisions when using

incomplete and inaccurate data. Fuzzy logic is particularly useful when using fuzzy sets to identify overlapping disease types.

3.2 Description of the LPTEG method

The process of blood clotting is a cascade process. During blood clotting, the rheological properties of the blood change from a liquid state to a viscoelastic solid state. When we use the results of laboratory tests, we can only give an isolated assessment, and only integrated tests make it possible to consider the entire set of interaction of elements of the hemostatic system when evaluating the hemostatic potential.

For our experiment, when developing a method for assessing the hemostatic potential using fuzzy logic, the method of low-frequency piezothromboelastography is used, since it shows the process of fibrinogenesis from the origin of the clot to the determination of the lytic activity of the test blood.

The LPTEG method involves the study of whole unstabilized blood and this reduces the errors of the preanalytic stage and increases the reliability of the results of the study (Figure 14)

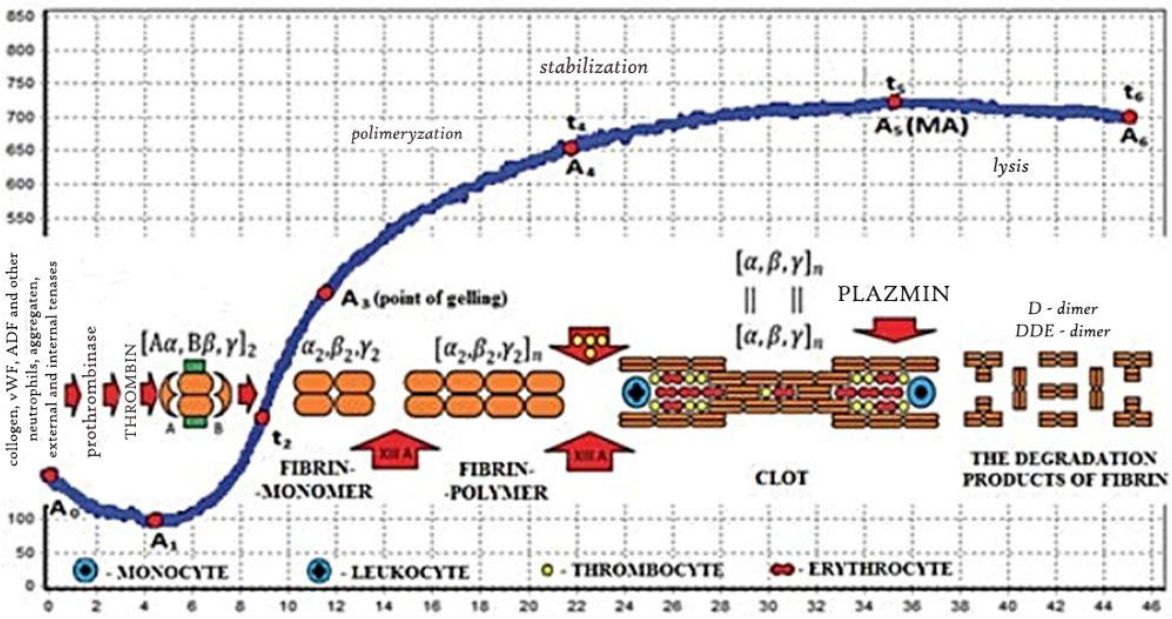


Figure 14 – Passage of all stages of fibrinogenesis on the LPTEG curve

The process of passing the stages of fibrinolysis on the LPTEG curve has the following intervals:

1. Interval from A_0-A_1 (on the LPTEG curve) – this is the stage of the origin of the clot. This stage indicates the reaction of the plasma component of hemostasis (Figure 15).

2. Interval A_1-A_3 – a cascade of enzymatic reactions, due to which the activation of such coagulation factors as the factor IX, X, V. They promote the generation of thrombin and the production of fibrin.

Thus, in the inactive state, aggregation of fibrinogen molecules does not occur, since fragments A and B have a negative charge. Thrombin hydrolyzes the peptide bonds and during this process, the N-terminal fragments A and B are cleaved off and as a result, fibrin monomers are formed.

3. Point A_3 shows that the process of producing fibrin is over and a fibrin clot begins to form.

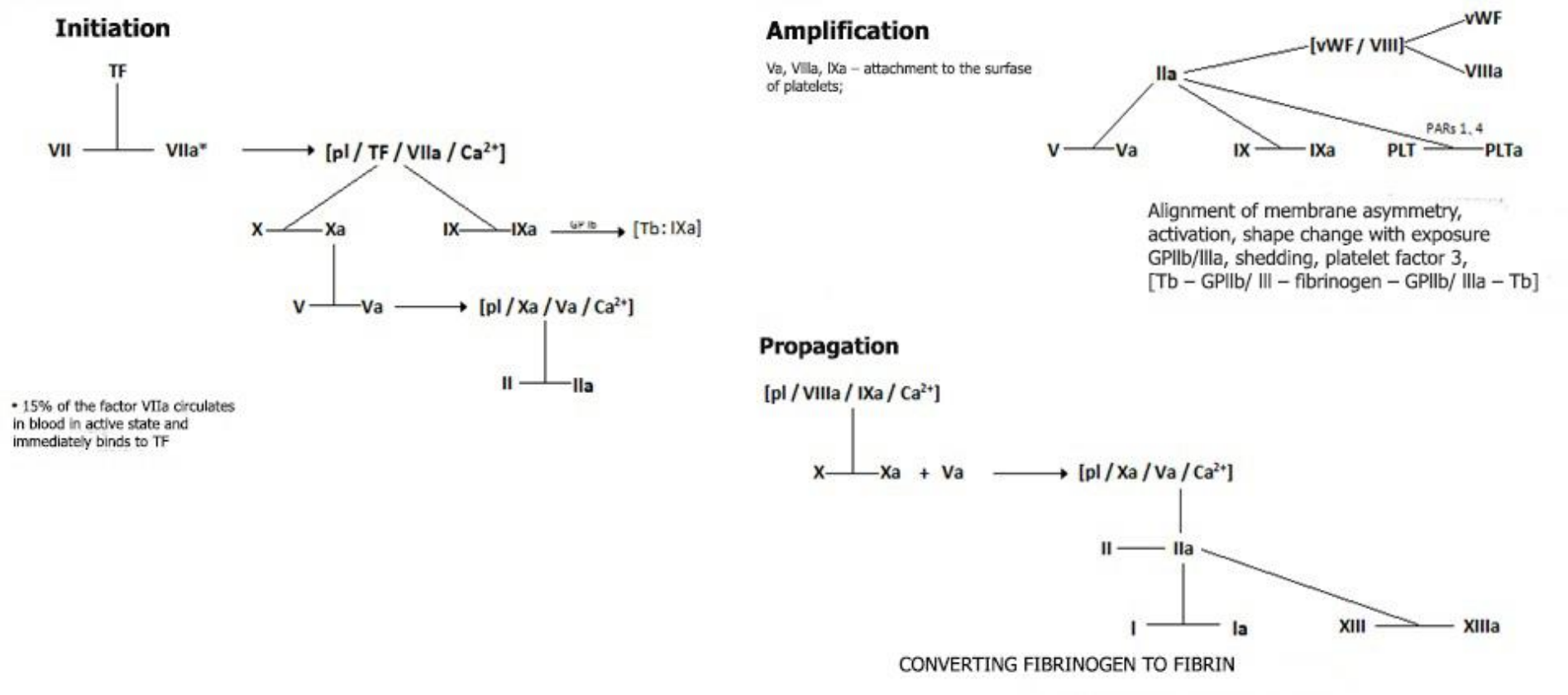
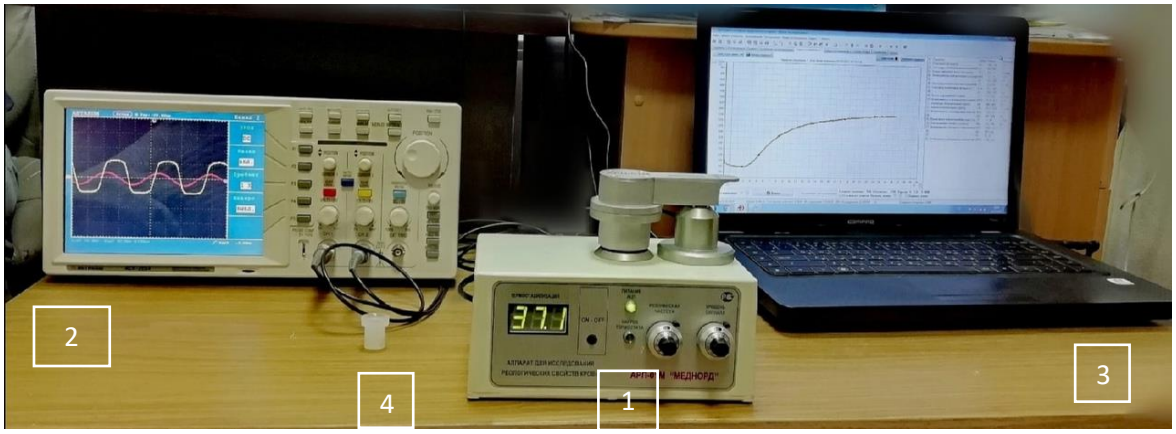


Figure 15 – Cascade of reactions of the plasma component of hemostasis

Figure 16 shows a setup for studying the amplitude-frequency and phase characteristics. The piezotromboelastograph ARP-01M "Mednord" registers the change in the resistance of the liquid to the resonant vibrations of the needle placed in the liquid. The needle, on the one hand, is fixed on top of the piezoelectric element, and the second side is placed in a cuvette with a liquid. When the needle is in a viscous liquid, the amplitude-frequency characteristics of the vibrations are shifted towards lower frequencies, depending on the parameters of the liquid and the frequency of forced vibrations [30, 32].



1 – piezotromboelastograph ARP-01M «Mednord»;

2 – oscilloscope; 3 – computer; 4 – test tube.

Figure 16 – Measurement of the amplitude-frequency and phase characteristics of the piezoelectric sensor

The main property of changes in the viscoelastic properties of blood during clotting will be an increase in the concentration of fibrinogen, as a result of a cascade of reactions (Figure 17). The initial concentrations of the factors involved in the coagulation process are shown in Table 1 [43, 48, 50].

Table 1– Initial concentrations of the main coagulation factors (index "a" means activated factor)

Factor	Initial concentration (nM)
I	7000 (fibrinogen)
Ia	7.0 (fibrin)
II	1400 (prothrombin)
IIa	1.4 (thrombin)
V	20
Va	0.02
VIII	0.7
VIIIa	0.0007
IX	90
IXa	0.09
X	170

The reaction of fibrin formation after the interaction of fibrinogen with thrombin is the main reason for the increase in blood viscosity during its clotting. Thus, the LPTEG curve describes the dynamics of changes in blood viscosity [48, 49].

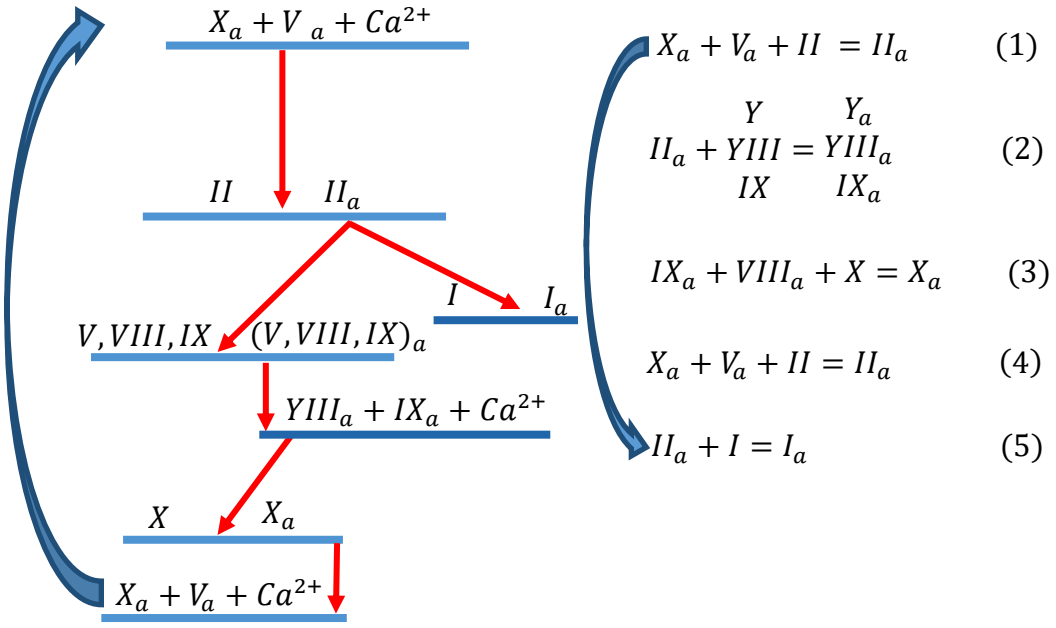


Figure 17 – Cascade of the main biochemical reactions of blood clotting in the initial phase of fibrinogenesis

Following from the kinetic equation of fibrin formation (5), we should write

$$\frac{dN(I_a)}{dt} = N(II_a) \times N(I) \times R_{I,II} = \alpha \frac{d\eta}{dt}, \qquad (6)$$

where $N(II_a); N(I)$and $N(I_a)R_{I,II}$ – concentrations of activated thrombin, fibrinogen, and fibrin,

$R_{I,II}$ – the rate of the corresponding biochemical reaction;

α – the proportionality coefficient between the LPTEG signal curve and the rate of change in blood viscosity;

η – dynamic blood viscosity index.

Thus,

$$N(II_a) = \frac{\alpha}{N(I) \times R_{I,II}} \frac{d\eta}{dt} \qquad (7)$$

Thus, knowing the dynamics of changes in the coefficient of dynamic viscosity of blood $\eta(t)$, it is possible to determine the concentration of thrombin at all stages of fibrinogenesis.

3.3 A physical and mathematical model for determining the coefficient of dynamic viscosity

The LPTEG method is necessary for the study of blood by changing the viscosity-elastic characteristics due to mechanical action on it and the analysis of the resulting shear deformations obtained using ultrasound diagnostic scanners.

In conducting such studies, it is particularly important to attract knowledge about the physical properties of blood, since its aggregate state changes during clotting, with significant changes in its viscoelastic properties [30].

To account for the viscous and elastic properties of blood, we used the method of complex representation of the viscosity modulus $\eta^* = \eta' + i\eta'',$ where $\eta', \eta'' -$ the coefficient of viscosity and the coefficient of elasticity associated with the shear modulus G': $\eta'' = \frac{G'}{\omega}$, where $\omega -$ frequency of shear stresses.

When the needle-resonator of a piezoelectric sensor is immersed in a cuvette with blood, the amplitude-frequency and phase characteristics of its oscillations shift towards lower frequencies, depending on the viscoelastic parameters of the liquid and the frequency of forced oscillations. To find this dependence, we used the theory of forced mechanical vibrations of a rod in a viscous liquid perpendicular to its axis in the laminar flow approximation. As a result, the modulus of the complex viscosity coefficient η^*, taking into account the relations $\eta'' = \frac{G'}{\omega}$, can be calculated by the formula [44]:

$$\eta^* = \sqrt{\eta'^2 + \left(\frac{G'}{\omega}\right)^2}, \quad (8)$$

Thus, experimental data on the measurement of the amplitude-frequency and phase characteristics of the rod vibration in a liquid allow us to determine its viscoelastic characteristics (G', η').

Figure 18 shows the results of an experiment to measure the oscillation amplitude of a piezoelectric sensor needle-resonator (blue curve) for a healthy volunteer.

The relative decrease in the amplitude $\frac{A'}{A}$ at the initial moments of time occurs due to the shift of the natural frequency of oscillation of the resonator needle from its resonant value, we can express by the formula:

$$\frac{A'}{A} = \frac{\alpha}{\omega_0} \frac{1}{x(t)\sqrt{(1-x(t)^2)}} \ , \qquad (9)$$

where $\omega_0 -$ natural frequency of oscillation of the resonator needle in the air; $x(t) = \frac{\eta}{2(G/\omega_0)}$.

The red curve in Figure 18 reflects the behavior of the measured oscillation amplitude of the resonator needle, adjusted for a decrease in its oscillation amplitude, taking into account the shift of the natural frequency. Calculations have shown that the effect of the frequency shift is noticeable in the first moments of time t≈3 min., during which the time of fibrin production is insignificant and does not affect the increase in the blood viscosity coefficient.

Obviously, the time point t_1, corresponds to the situation when two competing processes: the natural frequency shift and the operating time of the fibrin are compared in magnitude. At $t>t_1$, an increase in the concentration of fibrin strongly affects the increase in the viscosity coefficient n. Figure 18 shows that the red and blue curves at t>10 min almost coincide.

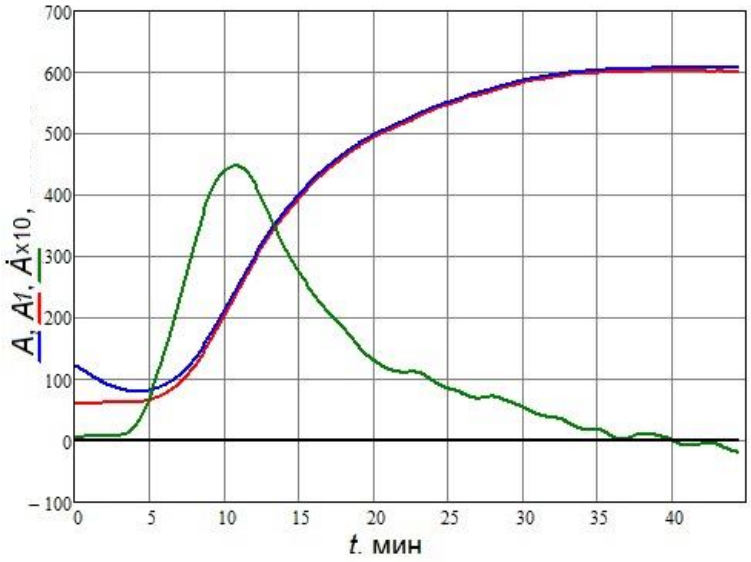


Figure 18 – The behavior of the integrative curve of the LPTEG as a function of time

The green curve in Figure 18 indicates the change in the concentration of thrombin in rel. units, determined from formula (4). We see that at the first moments of time, the increase in the concentration of thrombin is insignificant and linearly depends on time, but after 3 minutes, a nonlinear growth (generation) of thrombin is observed, which corresponds to the inclusion of positive feedback in the cascade of enzymatic reactions. The concentration of thrombin reaches a maximum at time t_2, at which the second time derivative of the integrative curve is zero.

$$\frac{dNIIa}{dt} = \frac{\alpha}{NI \times R_{I,II}} \frac{d^2\eta}{dt^2} \tag{10}$$

Thus, the t_2 point is the inflection point at which the exponential growth of the fibrin concentration slows down [46].

3.4 Neuro-fuzzy model for HP estimation

When conducting studies using the LPTEG method in different patients, the curves differ significantly from each other, and in some cases even intersect. In order for us to process the data correctly, we must apply the fuzzy logic method.

The study of integrative blood coagulation curves using the LPTEG method on groups of healthy and groups of sick people shows that the LPTEG curve reflects the difference in HP.

This is due to differences in the aggregate state of the blood, which determines the level of HP. However, in many cases, the LPTEG curves related to different levels of HP do not show noticeable differences between them. Increasing the statistical sample to clarify the diagnosis of the disease does not lead to success, because the groups of curves belonging to different levels of HP overlap.

In addition, the analysis of one specific case of the disease according to the LPTEG curve does not provide an unambiguous solution for determining the diagnosis.

The solution to this problem was a neuro-fuzzy model with three layers:

– first layer includes input features (patient complaints, symptoms, and other data related to the assessment of hemostasis);

– second layer is the construction of a database of rules that will be used to classify the types of HP.

– third layer is the three subtypes of the hemostatic system (hypercoagulation, normocoagulation, and hypocoagulation).

To evaluate the hemostatic system, we need to collect complete information about fibrinogenesis and the LPTEG method shows this. The analysis of the curves makes it possible to calculate the concentrations of fibrin and thrombin, which is fundamental in determining the level of hemostatic potential.

Thus, of the many possible factors, the most significant is the concentration of fibrin. Accordingly, to construct the mathematical apparatus of fuzzy logic, we must take four input variables. As input variables, these are the data of the input values, since the initial stages of coagulation, at which the production of fibrin occurs, are most

important to us. Especially the point t_2, which shows the maximum generation of thrombin [20, 32, 46, 47].

The first pair of input variables: t_1 and t_2 (corresponding to the position of the amplitude of the piezothromboelastography signal and the amplitude at the inflection point of the coagulation curve).

The second pair: A_1 and A_2 (corresponding to the time for the signal amplitude values A_1 and A_2).

We will assign term sets consisting of three fuzzy values to each input parameter: "small", "medium", and"large". Intervals of values were defined for these term sets.

As an output parameter, we select the hemostatic potential that has such term sets: "low", "normal", "high".

The main step in creating a fuzzy neuro-fuzzy model is to create a rule base that should reflect the basic principle: "If the LPTEG curve shifts to the left and has a large amplitude, then the indicators shift towards hypercoagulation, and if the curve shifts to the right and the amplitude is low, then this indicates the presence of hypocoagulation." To create logical rules, the minimum and maximum points were used in the analysis of the obtained LPTEG curves, as well as with the assistance of medical experts.

Building logical rules for a fuzzy neuro-fuzzy model in a table 2.

Table 2 – Rule Base

№	Rule Description
1	**IF** (A_1 is high) and (t_1 is low) **then** (HP is giper)
2	**IF** (A_1 is middle) and (t_1 is middle) **then** (HP is norma)
3	**IF** (A_1 is low) and (t_1 is high) **then** (HP is gipo)
4	**IF** (A_2 is high) and (t_1 is low) **then** (HP is giper)
5	**IF** (A_1 is middle) and (t_1 is middle) **then** (HP is norm)
6	**IF** (A_1 is low) and (t_1 is high) **then** (HP is gipo)

All calculations and program development were carried out using the MATLAB 2015b package, the FUZZY LOGIC TOOLBOX module.

The model consists of the following steps:

1. Input and output data were entered in the program (Figure 19).

2. For the selected pairs of input variables (A_1, A_2, t_1, t_2), the terms of the set of their three fuzzy values were determined: small, medium, and large (Figure 20).

3. The output variable is defined as the hemostatic potential, with three values of the term sets of fuzzy values: low, normal, and high (Figure 21).

4. A rule base was compiled, which consists of six rules (Figure 22). For example: «If A_1 is a small value and t_1 is a high value, then HP is high».

At the output, we get an estimate of the hemostatic potential (how high is the probability of changing the HP in one direction or another) [44].

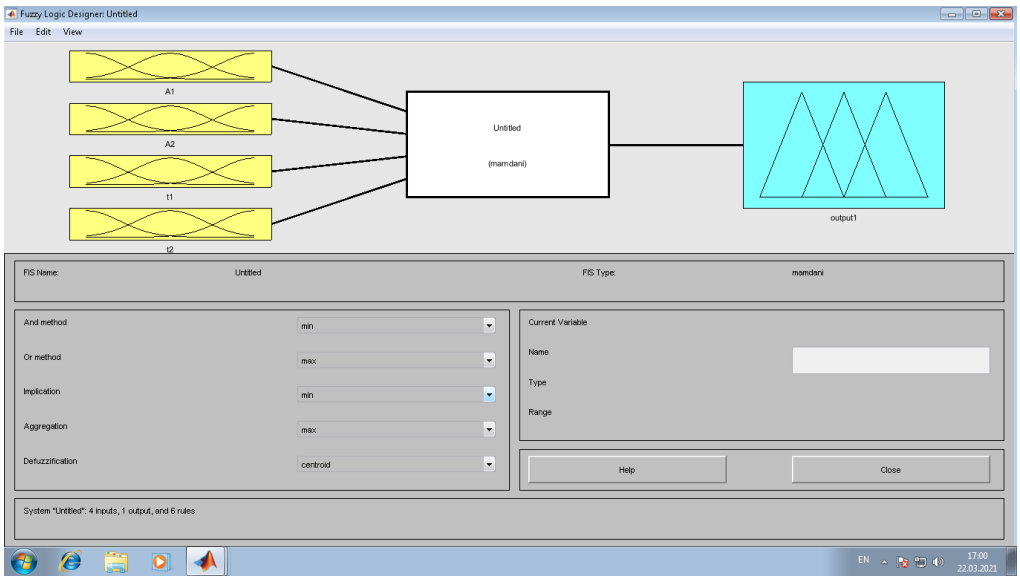


Figure 19 – General scheme of input and output data for assessing the hemostatic potential

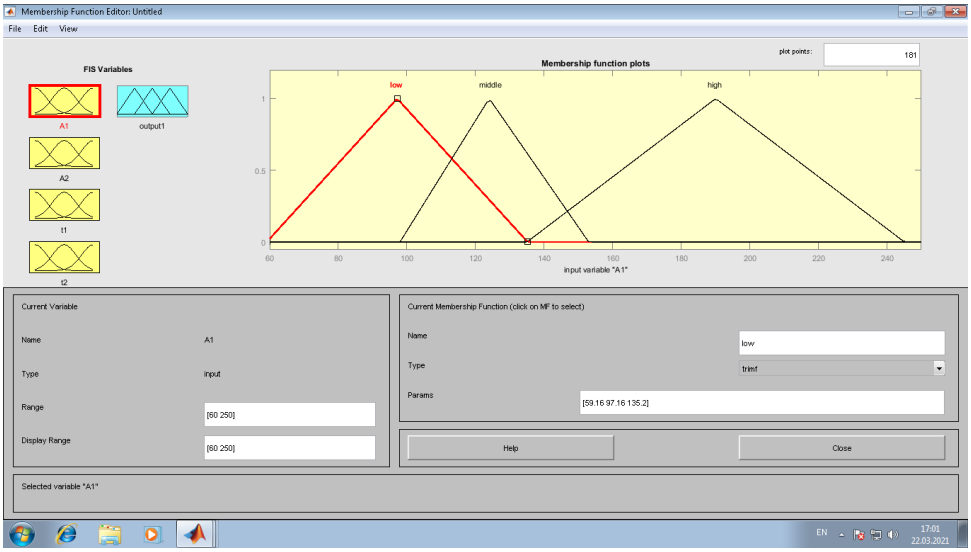


Figure 20 – Editor window for membership functions and definition of term sets for one of the input data

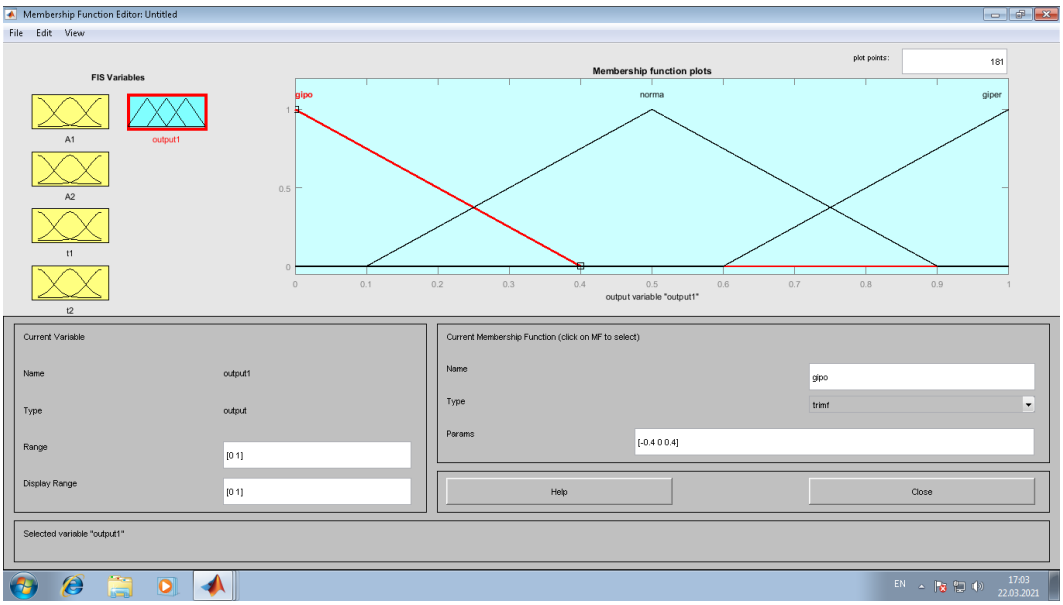


Figure 21 – Defining the membership functions for the output data

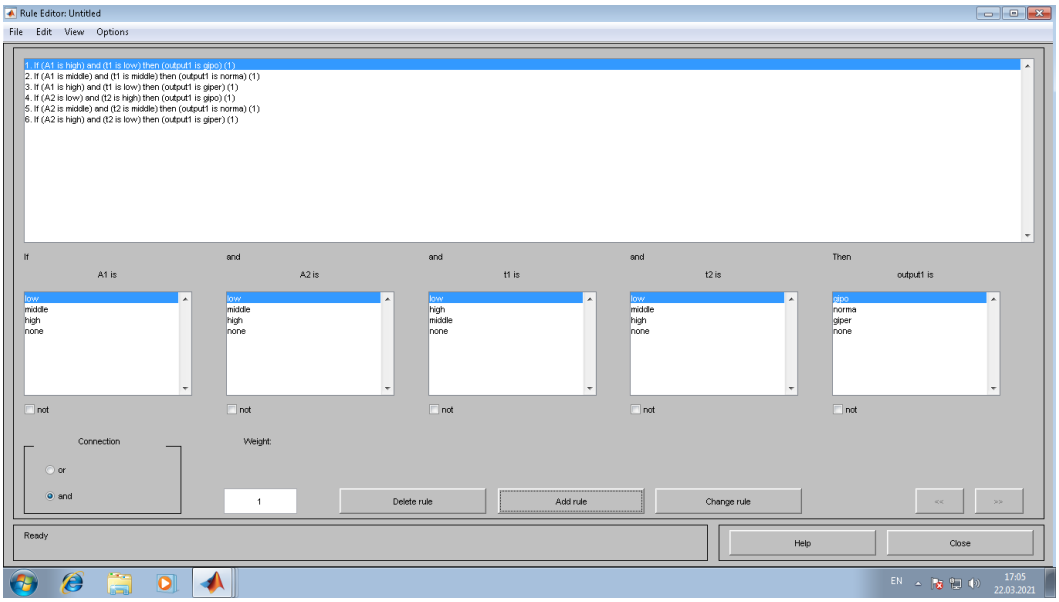


Figure 22 – Creating a rule base in the FUZZY LOGIC TOOLBOX module

This system is convenient for specialists, because it is quite easy to use. In the program, you only need to enter the data of the LPTEG curves and the program automatically shows the level of hemostatic potential.

Thus, the fuzzy model makes it possible to determine the level of hemostatic potential and perfectly complements the LPTEG method, reducing the study time and helping to work with inaccurate and fuzzy data.

3.5 Approbation of the HP estimation method using the fuzzy logic apparatus

We conducted a blood test at the E. D. Goldberg Research Institute of Pharmacology and Regeneration. The experiment involved patients with ischemic disease, hemophilia and conditionally healthy volunteers.

Each group consisted of 20 people and the main criteria for inclusion in the group were the age from 30 to 60 years, a verified diagnosis for patients, and the participants must have signed an informed consent to participate in the experiment.

The main criteria for inclusion in the group of volunteers were the age from 30 to 60 years, the absence of confirmed diagnoses and the mandatory signing of the consent of the volunteer for inclusion in the study.

To study the state of the hemostatic potential for all three groups, we conducted a study of hemostasis using the method of low-frequency piezothromboelastography.

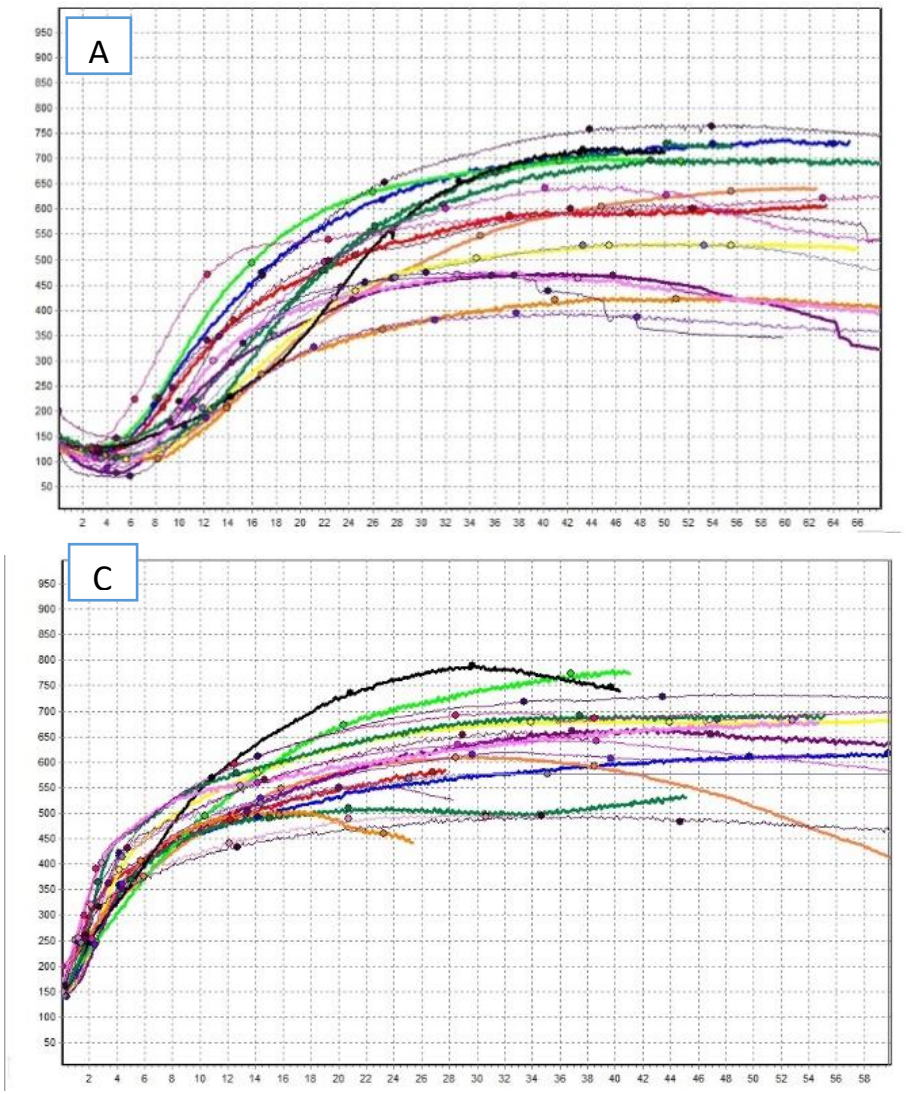
The procedure was performed by taking whole unstabilized blood taken without using a tourniquet and then placing the blood in the cuvette of the Mednord device.

The test of low-frequency piezothromboelastography showed us a significant spread of curves in each of the presented groups. This variation is due to the difference in the biochemical parameters of the blood of each of the patients, and as can be seen from the figures, the graphs will shift to the left and up during the transition from hypocoagulation to hypercoagulation.

Figure 23 shows the obtained results of the signal amplitudes of the piezoelectric sensor in the process of whole blood coagulation in three groups of patients (20 people in each group). The first group of patients had coronary heart disease, the second group - patients with hemophilia and the third group-healthy volunteers.

When conducting the experiment necessary for constructing the mathematical apparatus of fuzzy logic, we chose the method of low-frequency piezothromboelatography, since it has a number of advantages over others and allows us to evaluate whole non-immobilized blood. In addition, this method shows the entire process from the beginning of the origin of the clot to its lysis.

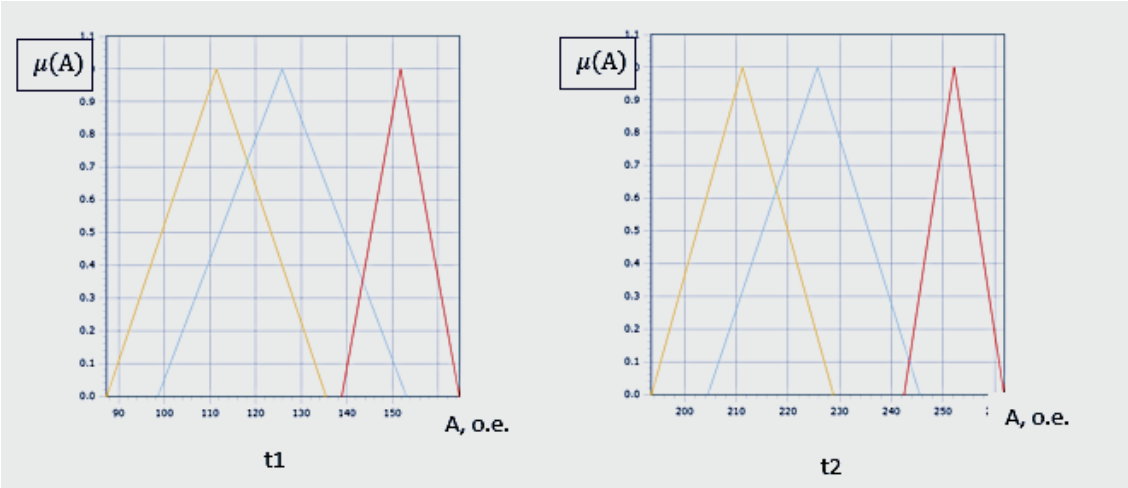
Statistical processing of the obtained results using the fuzzy logic apparatus was carried out using the data spread method (the law of three sigma). The data spread method assumes that the values of the membership function of the value X, which means the deviation of the signal amplitude from the average value, will be deferred along the ordinate axis. For the membership function, a triangular shape was used, constructed using the three Sigma rule [47].



A– hypercoagulation; B – normacoagulation; C – hypocoagulation.

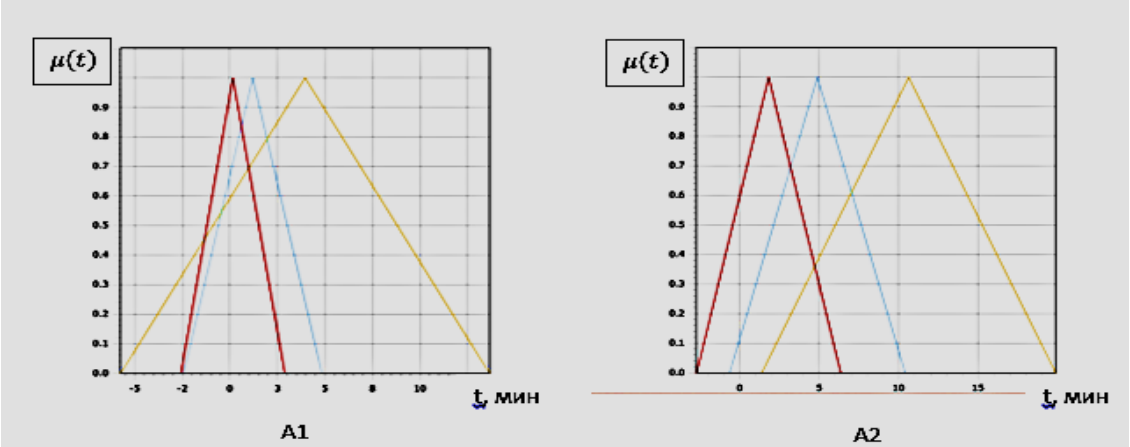
Figure 23 –The state of the hemostatic potential A of whole blood from the time of coagulation of patients

Figure 24-25 shows the statistical processing of data for characteristic times t_1 and t_2 and for amplitudes A_1 and A_2. These values indicate the deviation of the amplitude from the average value.



20 patients with reduced blood clotting
20 patients-healthy volunteers
20 patients with increased blood clotting

Figure 24 – Membership function $\mu(A)$ of the fuzzy set {A} - amplitudes of the piezoelectric sensor signal for time t_1 and t_2



20 patients with reduced blood clotting
20 patients-healthy volunteers
20 patients with increased blood clotting

Figure 25 – Membership function $\mu(t)$of the fuzzy set $\{T\}$ - amplitudes amplitudes $A_1$and A_2

The membership functions that we constructed confirmed our theory about the fuzziness and inaccuracy in deciding on the level of hemostatic potential and determining certain pathologies.

3.6 Results of testing a neuro-fuzzy model of the process for assessing the hemostatic potential

To test the fuzzy neuro-fuzzy model, we conducted an experiment in which 15 people participated. As a result, the group of patients with hypocoagulation consisted of six people, the group of healthy people consisted of five people and the volunteers with hypercoagulation consisted of four people. The LPTEG curves are shown in Figure 26.

In order to test the neuro-fuzzy model, we studied the curves of each person from the control group. Figure 27 shows the curve of one of the patients. This curve shows the indicators at points A_1, A_2, t_1, and t_2. These indicators were entered into the program for testing the model.

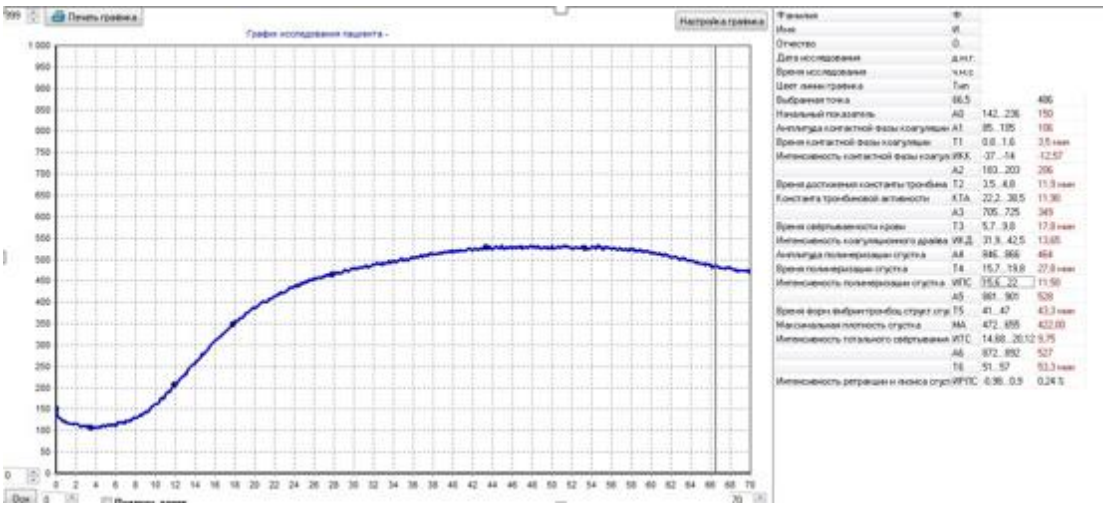
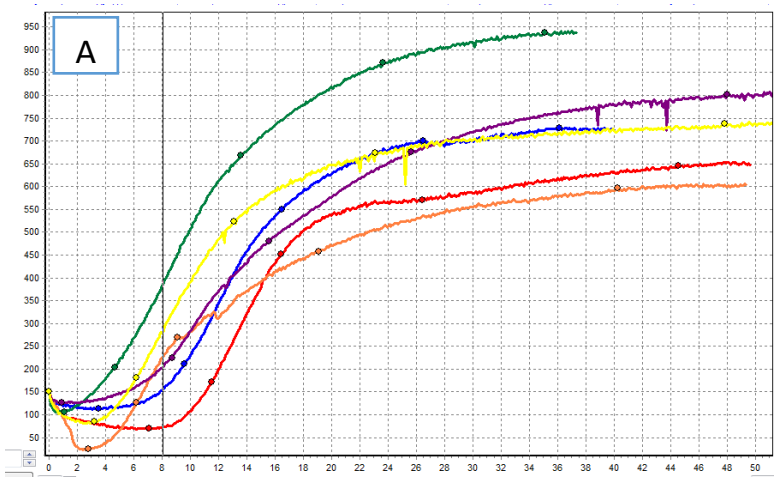
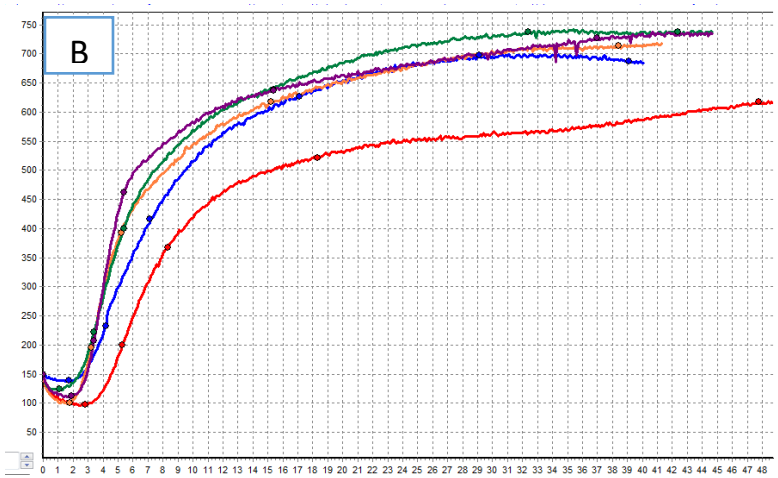
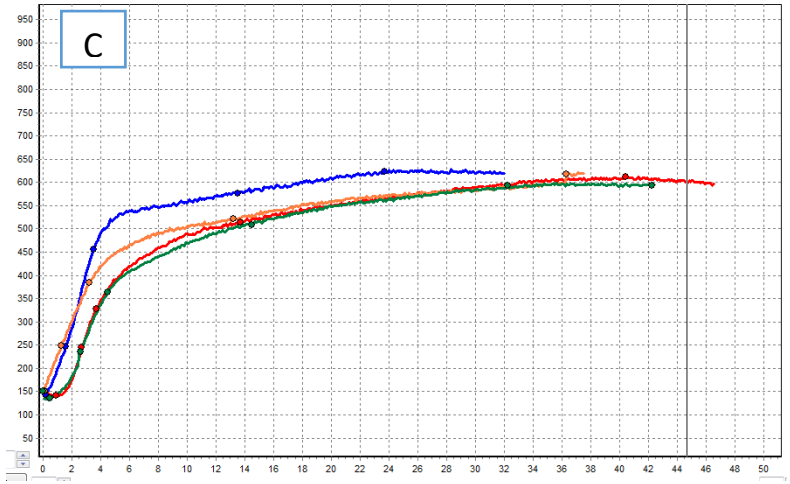


Figure 27 –The LPTEG curve of one of the volunteers







A – hypocoagulation; B – normacoagulation; C – hypercoagulation.

Figure 26 – The state of the hemostatic potential of whole blood from the time of coagulation of patients

The study of the obtained results of the control experiment helped to adjust the membership functions in the developed program. The interval boundaries were adjusted and the rule base was adjusted.

Figure 28 shows the results of calculating the patient's HP based on experimental piezothromboelastography data processed using fuzzy logic. The HP level is 0.805. This means that the patient has impaired indicators of the balance of the coagulation and anticoagulation systems and the risk of thrombosis is high. To normalize the coagulation, this patient needs corrective treatment. If we follow the results of the LPTEG curve, the HP data for this patient were borderline and showed a HP slightly above average. Additional tests also showed deviations from the norm in the direction of hypercoagulation. Therefore, the use of the fuzzy logic method for borderline situations allows us to establish the correct diagnosis of HP [51].

Thus, the processing of the experimental data of the LPTEG for the key values of the amplitude A (t1), A (t2) at time points (t_1, t_2), the signal of the piezoelectric sensor of the piezotromboelastograph using fuzzy logic and the corresponding base of logical inference rules gives, as a result, a decision on the level of the hemostatic potential.

Figure 29 shows a 3D function that shows the dependence of the output variable (the level of the hemostatic potential) on the input data (the values of the amplitude A (t1), A (t2) at time points (t_1, t_2)).

Using the indicators of the level of hemostatic potential, we can make a choice of tactics:

1. If the level of hemostatic potential is low (from 0 to 0.49), then the anticoagulation system prevails and the tactics that regulate the risk of bleeding are chosen.

2. If the HP level is average (0.5 - 0.6), then the coagulation system is balanced with the anticoagulation system and the person is healthy.

3. If the HP level is high (0.6-1), then the coagulation system prevails and tactics are required to reduce the risk of thrombosis.

The practical application of the developed neuro-fuzzy model for determining the level of HP helps to reduce borderline cases and allows for correct diagnosis.

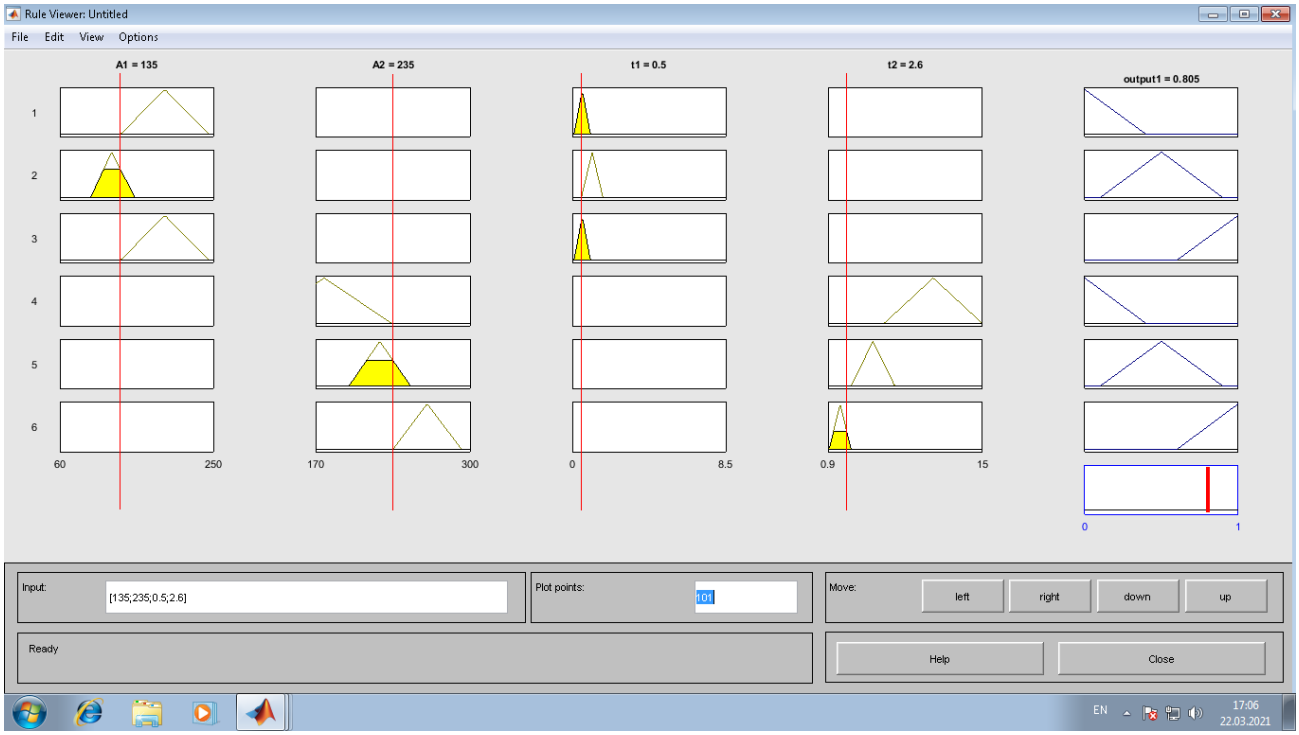


Figure 28. Window for viewing the rules and determining changes in the level of hemostatic potential

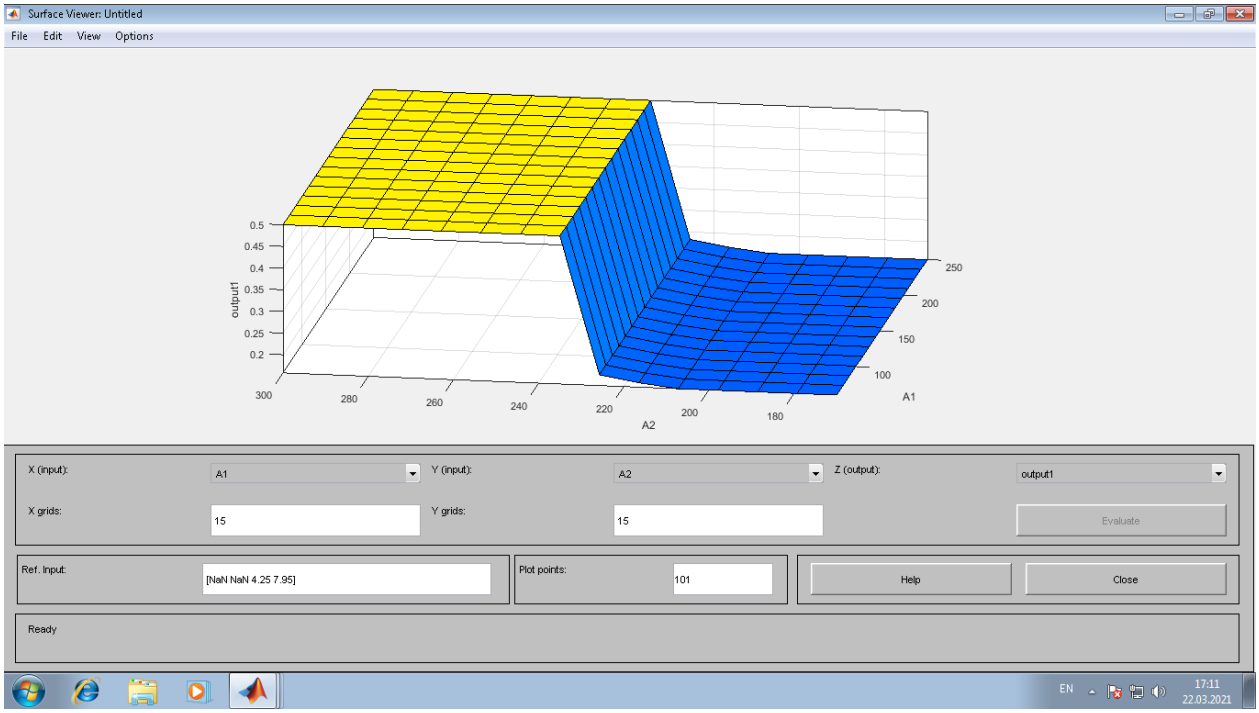


Figure 29. 3D function of the dependence of the output variable on the input

Thus, our studies have confirmed the practical significance of using fuzzy logic in the assessment of hemostatic potential, for borderline cases with overlapping data classes, which makes it possible to more likely interpret the results of clinical trials and improve the quality of the decision-making process.

CONCLUSION

As a result of the work performed, the planned tasks were solved and the following results were obtained:

1. Modern methods of assessing the hemostatic potential are studied;

2. The method of fuzzy logic in the medical decision support system is studied;

3. Experiments were conducted to assess the hemostatic potential and identify cases of hypo -, hyper-and normocoagulation;

4. Experimental studies of the viscoelastic characteristics of blood were carried out;

5. A mathematical model for estimating the hemostatic potential using the theory of fuzzy sets is developed;

6. A neuro-fuzzy model was tested to assess the hemostatic system in different clinical situations.

The introduction of classes with inaccurately defined boundaries is the basis for the development of a flexible approach to modeling complex physical systems, for example, when modeling the hemostasis system.

The use of fuzzy logic in medicine has proven to be an effective method that allows you to make informed diagnostic decisions based on incomplete and inaccurate data, since the rules of fuzzy logic allow you to work with overlapping (overlapping) types of diseases.

During the study, we provided a justification for choosing the method of low-frequency piezothromboelastography, since this method provides information at all stages of coagulation from initiation to the formation of a fibrin clot. This method shows that the initiation phase in the process of fibrinogenesis has a non-monotonic dynamics of changes in the viscoelastic properties of blood, which increases its rheological properties.

The method of assessing the hemostatic potential involves statistical analysis of the curve of the NPTEG test, but the processing of the obtained data often shows overlapping data, which required neuro-fuzzy analysis of this data using fuzzy logic.

We have shown that the dynamics of viscoelastic characteristics on the curve of low-frequency piezothromboelastography reflects the dynamics of processes occurring in the blood. Analysis of the curve allowed us to calculate the concentrations of thrombin and fibrin, which in turn are key in assessing the hemostatic potential.

The application of the mathematical apparatus of fuzzy logic to data processing based on a statistical sample of patients allowed us to build a neuro-fuzzy model of the hemostasis system and use it in different clinical situations.

To construct the neuro-fuzzy models, the key parameters that determine the dynamics of the fibrin production were selected, and triangular membership functions for the signal amplitudes for time t_1 and t_2 were constructed .

For the selected pairs of input variables, the term sets of three values are defined: small, medium, and large.

The output variable was the hemostatic potential, which has three term sets in the program: low, normal, and high.

Calculations have shown that the use of the fuzzy logic method significantly increases the reliability of the diagnosis.

Thus, the study and comparison of the results showed that the new approach to the assessment of hemostatic potential makes it possible to interpret the result most accurately and improve the quality of the decision process when making a diagnosis.

The main scientific significance of the results lies in the fact that the developed method for assessing the human hemostatic potential using the theory of fuzzy sets contributes to improving the diagnosis of the hemostatic system.

Based on the results of the work, two articles were prepared and submitted to the press and 3 reports were made at international conferences.

REFERENCES

1. Barkagan Z. S., Momot A. P. Diagnostics and controlled therapy of hemostatic disorders. – M. Newdiamed, 2008. – 292 p. (in Russian)

2. Phuong NH, Kreinovich V. Fuzzy logic and its applications in medicine. Int. J Med Inform. 2001 Jul; 62(2-3):165-173. Doi: 10.1016/s1386-5056(01)00160-5. PMID: 11470619.

3. Davvaz B. and Sadrabadi E. H. An application of intuitionistic fuzzy sets in medicine// International Journal of Biomathematics. – 2016. – Vol. 9. – № 3. – P. 15. doi.org/10.1142/S1793524516500388.

4. Svirin P. V. Laboratory diagnostics of hemostatic disorders. – Moscow: Tver: OOO "Publishing House "Triada", 2005. – 227 p. (in Russian)

5. Serebriyskiy I. I. Global and "local" tests of the hemostasis system in the diagnosis of hypercoagulation syndrome / / "Handbook of the head of the clinical and diagnostic laboratory". – 2012. – №. 12. – p. 27-34. (in Russian)

6. Stuklov N. I. Research of the hemostasis system in a modern laboratory / N. I. Stuklov, G. I. Kozinets // Clinical laboratory diagnostics. – 2007. – №. 9. – p. 52-53. (in Russian)

7. Mustafin I. G., Kurmanbaev T. E., Schmidt A. A., Timoshkova Yu. L., Atayants K. M. Global "methods of research of the hemostasis system in modern obstetric practice" / / Kazan Medical Journal, 2019. – Vol. 100. – №. 6. – p. 958-964. Doi: 10.17816/KMJ2019-958

8. Bokarev I.N., Doronina A.M., Kozlova T.V. et al. Laboratornye metody issledovaniya sistemy svertyvaniya krovi. Metodicheskie rekomendatsii. 2-e izd. (Laboratory methods for studying the blood coagulation system. Guidelines.) Moscow: ATGPSS im. A. Shmidta–B.A. Kudryashova. 2011; 15. (in Russian)

9. Berkovskiy A.L., Babenko S.V., Suvorov A.V. Problemy standartizatsii v koagulologii. Laboratornoe soprovozhdenie. (Problems of standardization in coagulology. Laboratory support.) Moscow: Gematologicheskiy nauchnyy tsentr MZ RF. 2015; 45 p. (in Russian)

10. Tyutrin I. I. Low-frequency piezothromboelastography in the diagnosis of hemostatic disorders: method. Manual for doctors / I. I. Tyutrin, V. V. Udut, M. N. Shpisman. Siberian State Medical University. - Tomsk, 2013. – 68 p. (in Russian)

11. Tyutrin I. I., Udut V. V. Low-frequency piezothromboelastography of whole blood: algorithms for the diagnosis and correction of hemostatic disorders. Tomsk: Publishing House of Tomsk State University, 2016. – 170 p. (in Russian)

12. Demkin V. P., Melnichuk S. V., Udut V. V., Tyutrin I. I., Demkin O. V. Physical principles of the low-frequency piezothromboelastography method for studying the rheological properties of whole blood. // Izv. univ. Physics. – 2019. – V. 62. – № 6. – p. 47–56. (in Russian)

13. Normal physiology. Textbook for medical universities / K. V. Sudakov. - M. Med. inform. agency, 2006.

14. Kuznik B. I. System of hemostasis // Human Physiology / ed. by V. M. Pokrovsky, G. F. Korotko. – M.: Meditsina. 2000-T1. – 448 p.

15. Davie E.W., Fujikawa K., Kisiel W. The coagulation cascade: initiation, maintenance, and regulation. Biochemistry. 1991; 29: 10363-10370

16. Versteeg HH, Heemskerk JWM, Levi M, Reitsma PH. New Fundamentals in Hemostasis. Physiol Rev 93: 327–358, 2013.

17. Shiffman F. J. Pathophysiology of blood / F. J. Shiffman, trans. from English. edited by Yu. V. Natochin. M.: "BINOM Publishing House". - 2007. - 448 p

18. Federal Directory of Laboratory Research. Directory of laboratory tests. – 2019. https://nsi.rosminzdrav.ru/#!/refbook/1.2.643.5.1.13.13.11.1080

19. Shpisman M. N., Tyutrin I. I., Udut V. V., Ripp E. G., Sorokozherdiev V. O. Realities and prospects of instrumental diagnostics of the functional state of the hemostasis system in the medicine of critical states. – 2009. – № 4 (2). – P. 189-194

20. Mustafin I. G., Kurmanbaev T. E., Schmidt A. A., Timoshkova Yu. L., Atayants K. M. Global "methods of research of the hemostasis system in modern obstetric practice" / / Kazan Medical Journal – 2019-Vol. 100. – № 6. – p. 958-964. Doi: 10.17816/KMJ2019-958

21. Serebriyskiy I. I. Global and "local" tests of the hemostasis system in the diagnosis of hypercoagulation syndrome // "Handbook of the head of the clinical and diagnostic laboratory". – 2012. – No. 12. – P. 27–34. (in Russian)

22. Stuklov N. I. Research of the hemostasis system in a modern laboratory / N. I. Stuklov, G. I. Kozinets // Clinical laboratory diagnostics. – 2007. – No. 9. – p. 52–53. (in Russian)

23. Kathleen E., Ziedins K.B., Wolberg S.A. Global assays of hemostasis. J. Curr. Opin. Hematol. 2014; 21 (5): 395–403. DOI: 10.1016/j.jcrc.2013.10.010

24. Kurmanbaev T.E., Yakovlev N.V., Khasanov A.A. et al. Modern methods for assessing the status of the hemostatic system in obstetrics. Aspirantskiy vestnik Povolzh′ya. 2016; (5–6):68–73. (In Russian.)

25. Ataullakhanov F.I., Balandina A.N., Vardanyan D.M. et al. Primenenie testa trombodinamiki dlya otsenki sostoyaniya sistemy gemostaza. Uchebnoe posobie. (The use of thrombodynamics test to assess the state of the hemostatic system. Tutorial.) Ed. by A.M. Shulutko. Moscow: Pervyy Moskovskiy gosudarstvennyy meditsinskiy universitetim. I.M. Sechenova. 2014; 85 p.

26. Thromboelastographic coagulation monitoring during cardiovascular surgery with the ROTEG coagulation analyzer / A/ Calatzis [et al.] // J. Hanley & Betfus. – 2000. P. 215-226. Doi: 10.1177 / 1076029618790092

27. Avdushkina L. A., Vavilova T. V., Zybina N. N. Method of thromboelastography / Thromboelastometry in the assessment of the hemostasis system: past and present. Reference intervals // Clinical and laboratory consultation. – 2009. – No. 5. – p. 26-33. Doi: 10.17749 / 2313-7347.2020.14.1.94-101

28. Tyutrin I. I. Low-frequency piezothromboelastography in the diagnosis of hemostatic disorders: method. Manual for doctors / I. I. Tyutrin, V. V. Udut, M. N. Shpisman. Siberian State Medical University. – Tomsk, 2013. – 68 p.

29. Demkin V.P., Mel'nichuk S.V., Udut V.V., Tyutrin I.I., Rudenko T.V., Krinitsyna D.B. Determination of Viscoelastic Characteristics of Whole Blood Based on the Low-Frequency Piezotromboelastography Method // Russian Physics Journal, 2020. – Vol. 62, № 12. – pp. 2219 – 2227. Doi: 10.1007/s11182-020-01969-w

30. Demkin V. P., Melnichuk S. V., Rudenko T. V., Tyutrin I. I., Udut V. V. Analysis of Viscoelastic Parameters of Fluids by Low-Frequency Piezoelastography // Bull. Exp. Biol. Med, 2020; 168 (3): 413-417. Doi: https://doi.org/10.1007/s10517-020-04721-z

31. Tyutrin I. I., Udut V. V. Low-frequency piezothromboelastography of whole blood: algorithms for the diagnosis and correction of hemostatic disorders. Tomsk: Publishing House of Tomsk State University, 2016. – 170 p. (in Russian)

32. Demkin V.P., Melnichuk S.V., Udut V.V., Demkin O.V., Tyutrin I.I. Physical principles of the method of low-frequency piezothromboelastography for studying rheological properties of whole blood // Russian physics journal, 2019. – Vol. 62. – №6. – P. 972–983. Doi: 10.1007/s11182-019-01803-y.

33. Zadeh L.A. Fuzzy sets as a basis for a theory of possibility // Fuzzy sets & Systems. – 1978. – Vol.1. – № 1. – P. 3–28.

34. Ryzhov A. P. Elements of the theory of fuzzy sets and its applications. - Moscow. - 2003. - 81 p.

35. Kobrinsky B. A. Vagueness in medicine and the need to reflect it in expert systems // Doctor and information technologies, 2016. – No. 5. – P. 6–14.

36. Chernov V. G. Fundamentals of the theory of fuzzy sets. Training manual. Vladimir State University – Vladimir: Publishing house of the Vladimir State University. – 2010. – p. 96.

37. Eremina V. V., Gorozhanina Yu. A. Designing an expert diagnostic system based on fuzzy logic // Modern scientific research and innovation. – 2017. – № 6.

38. J.Greeda, A. Mageswari, R. Nithya. A study on fuzzy logic and its applications in medicine// International Journal of Pure and Applied Mathematics. Special Issue. – 2018. – Vol. 119. – № 16.– P. 1515 – 1525.

39. Drivotinov B. V., Apanel E. N., Novoselova II. A., Mastykin A. S. Fedulov A. S. Adaptive neuro-fuzzy model for differential diagnosis of subtypes of transient ischemic attacks. – 2007. – No. 2. – p. 102-105. (in Russian)

40. Gadzhiev D. N., Tagiyev E. G., N. D. Gadzhiev, Shikhlinskaya R. Yu. Application of a fuzzy mathematical model of decision-making in the choice of optimal

surgical tactics in patients with non-tumor obturation jaundice / / Kazan Medical Journal. Theoretical and clinical medicine. – 2018. – Vol. 99. – No. 3. – p. 439-447. Doi.org/10.17816/KMJ2018-439

41. Khamidova R. R. Application of a biotechnical system for intellectual support of the process of prescribing therapeutic nutrition to patients with atherosclerosis // Online journal "NAUKOVEDENIE". – 2018. – Vol. 9. – №3.

42. Ovchinkina T. V., Mitin V. V., Kuzmin A. A. Application of hybrid neural networks in prognostic models for assessing the functional state of the cardiovascular system. – 2013. – № 5.

43. LaCroix D.E. A reduced equation mathematical model for blood coagulation and lysis in quiescent plasma // International journal of structural changes in solids – Mechanics and Applications. – 2012. – Vol. 4. – P. 23 – 35.

44. Tsibulina A. O. Mathematical model of expert information system for assessing the quality of medical technologies // Information technologies: Materials of the 58th International Scientific Student Conference on April 10-13, 2020/ Novosibirsk State University. University – Novosibirsk: CPI NSU, 2020. – p.162. (in Russian)

45. Demkin V. P., Melnichuk S. V., Zavadovsky K. V., Khoryak M. N., Rudenko V. V., Suyundukova A. T., Kukartseva D. N., Tsibulina A. O., Udut V. V. Influence of dynamic blood viscosity on coronary blood flow in the stenosed section of the artery // Russian Physics Journal, 2021. (in Russian)

46. Demkin V. P., Udut V. V., Melnichuk S. V., Demkin O. V., Kotlovskaya L. Yu., Rudenko T. V., Tsybulina A. O., Zhukovskaya A. A. Test of thrombin generation based on the resonant-acoustic method for determining low-frequency viscoelastic properties of whole blood // Bulletin of Experimental Biology and Medicine. – 2021. (in Russian)

47. Tsibulina A. O., Kotlovskaya L. Yu., Demkin V. P., Udut V. V., Diagnostics of the state of hemostasis with the use of the theory of fuzzy sets // VII International Conference of Young Scientists: biophysicists, biotechnologists, molecular biologists and virologists-2020: Collection of tez. / ANO "Innov. Tsentrkoltsovo". – Novosibirsk: CPI NSU, 2020. (in Russian)

48. Morozov Yu. A. Test of thrombin generation in clinical monitoring of the hemostasis system // Thrombosis, hemostasis and rheology. – 2003. – №4 (16). – P. 30–35.

49. Mann K.G. et al. Models of blood coagulation // Blood Cells, Molecules, and Diseases. – 2006. – T. 36. – №. 2. – C. 108–117.

50. Weisel J.W., Litvinov R.I. Fibrin formation, structure and properties //Fibrous proteins: structures and mechanisms. – Springer, Cham, 2017. – P. 405–456. Doi: 10.1007 / 978-3-319-49674-0_13.

51. Tsibulina A. O. Application of a fuzzy neural network model for determining the hemostatic potential // Physical methods in natural sciences and materials science: Materials of the 59th International Scientific Student Conference on April 12-23, 2021 / Novosibirsk State University. – Novosibirsk: CPI NSU, 2021. (in Russian)

APPENDIX A
Indicators of low-frequency piezothromboelastography

Table A.1 – The basic Indicators

Indicator	The value of indicators
t_1	Reaction period: the time from the beginning of the experiment to the fixation of the minimum amplitude A_1 (characterizes the suspension stability of the blood)
t_2	Indicates the gelling point per minute (determined automatically, due to a change in the tangent (tg) of the angle of inclination of the curve by 60% relative to the abscissa axis
t_3	Time to reach the maximum amplitude (A_5)

APPENDIX B
Calculated indicators of the LPTEG

Table B.1 – Indicator values and their interpretation

Indicators	Indicator values
$ICC = \frac{A1-A0}{t1}$	ICC – the intensity of contact coagulation in relative units, where: A_1 – maximum decrease in the curve amplitude over the reaction period t_1; A_0 – the initial value of the curve amplitude at time t_0. This indicator reflects the aggregation activity of the shaped blood elements of the first and second phases of coagulation.
$ICD = \frac{A3-A1}{t3}$	ICD – the intensity of the coagulation drive (in rel. units.) A_3 – the magnitude of the curve amplitude at the gelling point; A_1 – the maximum decrease in the amplitude of the curve during the reaction period t_1. This indicator shows the proteolytic stage of the third phase of coagulation.
$CTA = \frac{A2}{t2-t1}$	CTA – constant of thrombin activity (in rel. units)) A_2 – increasing the amplitude of the curve by 100 oe. t_2 - time to reach the A_2 curve amplitude t_1 – the time from the beginning of the study to the minimum amplitude A_1. This is a criterion for assessing the intensity of the proteolytic stage of fibrin formation

Continuation of Appendix B

$IPC = \frac{A4-A3}{10\ min}$	IPC – the intensity of polymerization of the clot (in rel. units.). A_4 – the value of the amplitude after 10 minutes from the gelling point; A_3 – the value of the amplitude at the gelling point. This indicator characterizes the intensity of the polymerization stage. The interval of ten minutes is due to the fact that the formation of cross-covalent bonds goes through a long stage of post-gel formation.
$MA = A_5 – A_1$	MA – maximum clot amplitude (in rel. units)) A_5 – the maximum amplitude of the LPTEG recorded for 10 minutes; A_1 – the maximum decrease in the amplitude of the curve during the reaction period t_1. Characteristics of the maximum density of the clot due to the shaped elements of the blood and their qualitative and quantitative characteristics of cross-linked fibrin after the completion of polymerization and the retraction process.
$ITC = \frac{MA}{t5}$	ITC – the intensity of total coagulation (in rel. units) MA - the maximum amplitude of the clot, calculated by the formula $MA = A_5-A_1$; t_5 – time of formation of the fibrin-platelet structure of the clot
$ICRL = \frac{A5-A6}{A5} * 100\%$	Intensity of clot retraction and lysis A_5- maximum value of the amplitude of the LPTEG curve; A_6- the value of the amplitude of the LPTEG curve after 10 minutes from A_5 This indicator shows the totality of the action of plasmin, leukocyte proteases, and erythrocyte kinases, which are in a given volume of blood.

End of Appendix B

$CTAA=\frac{ICD}{IPC}$	CTAA – coefficient of total anticoagulation activity (in rel. units) $ICD = \frac{A3-A1}{t3}$ $IPC = \frac{A4-A3}{10\ min}$ The anticoagulation activity of the blood is a key element in the regulation of the clotting process and several groups of inhibitors function there. This indicator is necessary in order to indicate the peak values of the functioning of the anticoagulation system in the first and second phases of coagulation, as well as at the stage of proteolysis of the third phase before the start of the process of active polymerization of the clot.

Отчет о проверке на заимствования №1

Автор: Цибулина Анастасия
Проверяющий: Печерицын Алексей Анатольевич (pecher@phys.tsu.ru / ID: 443043)

Отчет предоставлен сервисом «Антиплагиат» - users.antiplagiat.ru

ИНФОРМАЦИЯ О ДОКУМЕНТЕ

№ документа: 44
Начало загрузки: 29.05.2021 18:29:01
Длительность загрузки: 00:00:03
Имя исходного файла: Master_s_Thesis_eng_Tsibulina_final (2).pdf
Название документа: Master_s_Thesis_eng_Tsibulina_final (2)
Размер текста: 82 кБ
Тип документа: Выпускная квалификационная работа
Символов в тексте: 84282
Слов в тексте: 12482
Число предложений: 882

ИНФОРМАЦИЯ ОБ ОТЧЕТЕ

Начало проверки: 29.05.2021 18:29:05
Длительность проверки: 00:00:10
Корректировка от 11.06.2021 07:31:00
Комментарии: не указано
Модули поиска: Интернет

ЗАИМСТВОВАНИЯ	САМОЦИТИРОВАНИЯ	ЦИТИРОВАНИЯ	ОРИГИНАЛЬНОСТЬ
2,16%	0%	0%	97,84%

№	Доля в отчете	Доля в тексте	Источник	Актуален на	Модуль поиска	Блоков в отчете	Блоков в тексте	Комментарии
[01]	1,59%	1,59%	http://vital.lib.tsu.ru/vital/access/services/Download/vital:10653/SOURCE01 http://vital.lib.tsu.ru	24 Янв 2020	Интернет	21	21	
[02]	0,57%	0,86%	http://vital.lib.tsu.ru/vital/access/services/Download/vital:10087/SOURCE01 http://vital.lib.tsu.ru	24 Янв 2020	Интернет	8	12	
[03]	0%	0,09%	Soft Computing in Industrial Applications || https://doi.org	12 Сен 2019	Интернет	0	1	Источник исключен. Причина: Маленький процент пересечения.

Отв. за проверку
сист. „Антиплагиат" Печерицын А. А.