УДК 616-093.75:[616-71+616.43]

METHODS AND MACHINERY OF ACCUMULATION OF DATA FOR NON-INVASIVE DIAGNOSTICS AND MONITORING OF DIABETES MELLITUS



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Abstract. By monitoring we mean permanent observation of blood sugar level what is extremely important to ensure taking medication on time for insulin-dependent patients. DM diagnostics by non-invasive technique has the following advantages: the test is quick and painless, there is no risk of HIV infection and different forms of viral hepatitis, it is safe for both patients and medical staff, and does not require complicated biochemical tests and medical supplies.

Key words*:* non-invasive, procedure, diabetes mellitus, optical methods, glycoproteins.

The purpose of the research is to develop and demonstrate technology and instrumentation for noninvasive (without blood sampling) diagnostics and monitoring of Diabetes Mellitus (DM). By monitoring is understood long-term observation of sugar-in-blood concentration allowing a prompt taking of medicine, which is particularly important for in-sulin-dependent patients.

The DM noninvasive diagnostics has the following advantages:

1 Quick and painless analysis procedure;
2 No risk of HIV-infections or viral hepatitis;
3 Safe procedure for patients and attending medical personnel;
4 No need to conduct complicated biochemical tests or use consumed materials.

Non-invasive optical methods of blood analysis imply no danger to patients. At correct choice of equipment and performance specifications, exposure of living tissues to optical radiation will never exceed levels to which patients are exposed in their everyday life (solar radiation, various lamps, etc.). In case of long-term exposure to optical radiation (e.g., for monitoring purposes), only a slight increase in temperature of the illuminated part of tissue may be observed.

Theoretically, the noninvasive optical methods allow in vivo determination of any blood components and other biologic fluids content using a priory information about their spectral characteristics. This shall focus research results obtained within the framework of the given project on solving of a diversity of urgent medical problems [1].

Accuracy of glycated hemoglobin and glucose concentration determination using the method developed may be slightly lower than that obtained through invasive methods available today. However, advantages of our approach, such as absence of traumatism, medical personnel and patient safety, express character and relatively low cost of the analysis, independence from chemical agents availability, acquisition of more information about patient’s physiological state in one analysis, possibility to conduct screening tests to reveal health level of large population groups, shall make its development not only urgent and expedient, but also socially important.

Urgency of the proposed project. Introduction and promotion of healthy life-style, early detection of diseases and prevention of their transfer to a chronic form represent a substantial reserve for improvement of health and life quality and are foreground tasks of community health protection.

Solution of these tasks very largely depends on the state of clinical-and-laboratory service of public health system. The development level of laboratory (clinical) medicine, which is one of the most science-intensive and resource-demanding branches of the public health system, may be an indicator of general development level and condition of public health service as a whole. The laboratory service shall provide public health service and patients with an objective, reliable and on-time information to evaluate health condition of individuals and large population groups.

High quality of laboratory and individual research is an integral part of the public health service system. In the context of medicine commercialization and formation of market approaches and relations, we shall bear in mind that these tendencies shall not lead to a decrease in the standard of education and level of research activities.

The development of inexpensive custom-made diagnostic equipment for individual use is an urgent issue in carrying out analyses for the population. It applies particularly to diagnostic equipment designed for testing sugar content in blood, wherein frequent analyses shall be carried out for insulin-dependent patients [2].

Diabetes Mellitus (D.M.) ranks third in the world after cardiovascular diseases and cancer in terms of mass character and severity. According to data acquired from various sources, there are 120 to 180 million diabetic patients in the world, which is 2-3% of all population of the planet. Tens of millions of people suffer from overlooked forms of diseases, or they may have prediabetes as their parents are diabetics. According to current predictions, every 15 years there is expected a double increase in number of patients. Among diabetic patients, about 10-20% are patients having insulin-dependent (type I) diabetes, who have need for a constant monitoring of the disease. Average life of DM patients from early childhood is 28 years. In the Republic of Belarus, there are about 130,000 diabetic patients registered on the books today, who require regular medical check-up. About 15% of them suffer from the most severe form – insulin-dependent diabetes, when sugar content in blood must be checked up to 7 times a day. It is a very traumatic operation in terms of methods currently applied and reflects compensation factor just over a short period of time. The most urgent task today is the development of inexpensive device for noninvasive DM monitoring, which enables a painless determination of sugar content in blood. There are no similar devices in the world.

The reason of incapacitation and high mortality of DM patients lies in late aftereffects of illness, which require enormous expenses of health protection system and social security. Early detection of D.M. patients would considerably reduce medical and social security costs. However, active early-stage DM case finding today is impossible due to high cost of laboratory and measuring equipment.

For DM detection and treatment, an adequate carbohydrate metabolism valuation is required. Glucose tolerance tests, glycemia control measurements on empty stomach, etc. are carried out for this purpose. All these parameters, however, define glycemia over a short period of time and are liable to considerable variations, which depend on a number of factors (such as age, stress, nutrition, body weight, etc.) and, therefore, require frequent duplicate measurements. In this regard, scientists began to study stable glucose-protein compounds – glycoproteins (GP), among which glycated hemoglobin became most widespread [3].

In blood analysis of diabetic patients, a relationship between increased content of glycated hemoglobin and glycemia level has been determined. The GP level reflects glycemia over a preceding long time period comparable with duration of protein molecule half-life in blood. However, in a number of diseases accompanied by changes in protein lifetime in blood, the incoming data may be distorted.

The task of no lesser importance in diabetes mellitus is monitoring of glucose which plays a key role in organism. Glucose content in blood is an extremely important indicator for certain body organs, including brain. In healthy people, concentration of glucose slightly changes as a result of metabolic activity, but in whole remains under tight natural control of organism. However, this system of self-control is impaired in a majority of diabetics. It is typical for insulin-dependent diabetics who have to artificially inject insulin to lower the content of glucose. Long-term supernormal exceeding of glucose content may affect the work of a number of organs and even cause patient's death. In this regard, people with impaired carbohydrate metabolism need frequent (several times a day) measurements of glucose concentration in blood.

Target setting. In order to obtain information about composition of blood, it is proposed to use optical (spectral) method, which in full measure realizes all advantages of non-invasive methods. The study of optical radiation and living tissue interaction provides for a very useful information about the subject of inquiry. Possibility to obtain both qualitative and quantitative information over a variety of samples makes this method most attractive for medical diagnostics and monitoring.

In selecting a spectral range of optical radiation, we shall take into account the availability of so-called "spectral windows", wherein living tissues have the lowest absorptive capacity. They exist in visible (red), near infrared and meddle infrared radiation spectrum. Within the same spectrum, glucose and glycated proteins have pronounced spectral characteristics [4].

As a result, the proposed project shall provide for the development of diabetes mellitus diagnostic and monitoring facilities of higher competitive power as compared with those available today owing to:

– Quick analysis and possibility to practically operate in real-time mode;
– Low cost of single blood analysis;
– Independence from chemical agents or test-bands;
– Painlessness of analysis, absence of traumatism;
– Safety for patients and attending personnel (including no risk of HIV-infections);
– Higher accuracy through application of pulse method for in vivo determination of blood properties;
– Use of up-to-date elemental and design-engineering base;
– Reduction of hardware costs through shifting hardware functions onto software system.

Methods and equipment of this type may be used in polyclinics when conducting screening tests to find out state of health of large population groups, in endocrinological dispensaries and clinics both at the Ministry of Health of the Republic of Belarus and abroad.

Technical Approach and Methodology. The current laboratory diagnostics uses invasive methods to determine the level of stable glucose linkage with various proteins, among which glycated hemoglobin gained the maximum ground. It reflects the level of sugar content in blood over a long preceding period of time and, therefore, finds extensive application in the assessment of sugar concentration in blood.

The participants to the project have obtained first encouraging results in detecting interrelation between spectra of light absorption and diffusion by biological tissues as well as glycated hemoglobin level and sugar content in blood. An in-depth research is needed to create a device for noninvasive monitoring of diabetes mellitus.

Accuracy and reliability of noninvasive measurements may be attained through the development of an up-to-date measurement procedure based on determination of glycated hemoglobin level in blood (which determines sugar content) and the creation on its basis of an inexpensive and easy-to-use device with precision of measurement insignificantly different from that of standard biochemical and spectrophotometric analyses.

In diagnostics of diabetes mellitus, to obtain objective information on carbohydrate metabolism, there is a need to fully use data both on glucose content and glycated protein content in blood. It should be noted that along with the measurement of glucose and GP content, a very important aspect would be to simultaneously receive information about hemoglobin derivatives and certain decay products in blood. It could provide a more complete picture of patient's metabolic status and increase accuracy of glycated proteins content determination.

By now, various in vitro methods for determination of glycated hemoglobin content in blood (colorimetric method, liquid chromatography, isometric focusing, etc.) and glucose content in blood (biochemical methods) have become a routine practice. Hardware for implementation of these methods is also available and introduced into medical practice. For effective Diabetes Mellitus screening in laboratories, very convenient methods for drawing, storing and transportation of blood samples have been developed. However, all these methods require sample preparation (sometimes, it takes a lot of time – about half an hour) and the use of chemical agents (often very expensive). Moreover, they are traumatic, cause discomfort to patients and involve a procedure too complicated to use by patients outside the laboratory.

To remove the latter disadvantage, a number of industrial companies created portable devices for home monitoring of glucose concentration based on reflectometer analysis of testerstrip. These devices largely simplify sugar control in blood both in laboratories and at home. However, they also require blood draw and regular purchase of special bundles of strips for testing.

Growing recent interest has been focused on the development of non-chemical methods of glucose monitoring. Today, socalled ex vivo methods are progressing rapidly, which provide glucose monitoring through implantation of amperometric biosensors into man's body. With these methods, however, a number of other problems arise, such as biocompatibility, infection risk, appearance of thrombus, etc. Meanwhile, in combination with other methods (e.g. microdialysis), these problems are solved and the methods are gaining ground and acceptance in medical practice.

At present, very active attempts are being made in the world to develop noninvasive methods for glucose testing, i.e. without blood sampling, and to make equipment for such measurements. The great interest in in vivo methods of blood analysis derives from the fact that they practically have no defects peculiar to other methods [5].

There is a whole number of references and literature describing various methods of how to get information on glucose content in blood without puncturing patient's skin. For instance, by analysis of glucose content in lacrimal liquid or cell liquid extracted through pores, which are artificially broadened using low electrical currents or ultrasound. However, i) data received by these methods are indirect and may not correspond to the true state, and ii) these methods require blood drawing and, therefore, are not noninvasive.

To the best of our knowledge, there are no works available today related to the task of noninvasive determination of glycated proteins.

Medical follow-up and maintenance under the project as well as engineering of medical-sanitary requirements for the information-measuring systems and devices in whole shall be carried out by medical personnel out of the project staff in compliance with the requirements for medical apparatus, EU Regulations and Standards set for noninvasive devices and State Standards of the Republic of Belarus. Engineering and sanitary-hygienic testing of prototypes shall be conducted by the Public Health Expertise and Test Center of the Republic of Belarus.

Technological approach and methodology in the development of the device for noninvasive monitoring of diabetes mellitus as applied to project tasks will have the following features:

1. Investigation of non-invasive sugar-content-in-blood evaluation techniques and selection of facilities for the implementation of devices:

– Experimental analysis of absorption spectrum of pure hemoglobin forms (oxy-, deoxy-, carboxy-, meta- and gly-cated hemoglobin) within the wave band under study using spectrophotometric methods in order to track further impact of these spectra upon blood samples spectrum shall be carried out. The accuracy of measurements shall be determined by spectrophotometer precision characteristics.

– The structure and algorithms of measurement process control shall be determined. Flow-graph of device operating control algorithm to perform measuring cycle of all parameters shall be approved. All algorithms will be presented in the form of flowgraphs and implemented in practice in the form of Moore discrete automations.

2. Development of methods for determination of hemoglobin forms and a technique for hardware noninvasive measurement of sugar content in blood:

–Software flow diagrams and algorithm schemes for the measurement process control subject to structural processor module and elemental base arrangement shall be developed.

–Embodiments of the proposed device engineering and design based on application of discrete automations, graph theory, theory of stepwise generation of mental actions, human engineering, applied and system programming, sys-tem and circuit engineering of computer execution units and blocks shall be examined.

–A technique for in vitro determination of major and minor hemoglobin concentrations according to the measuring results of diffuse reflection and transmission of blood in the spectral range under study shall be worked out.

3. Investigation of spectral reflection and transmission of light by blood samples and modeling of various device implementation schemes:

–Diffuse reflection and transmission spectra of light by blood samples with known content of various hemoglobin forms using spectrophotometry and biochemical analysis shall be investigated and comparative assessment made. The accuracy of the investigation shall be determined by precision properties of spectrophotometer and biochemical tests.

–Structural modeling of the device circuits shall be done to examine variants of light transmission and reflection by blood samples.

–Functional diagrams of measuring systems shall be developed. As an elemental base of devices, it is proposed to use programmable logic integrated circuits (Advanced Micro Devices (AMD), Altera, Xilinx, Atmel, Intel, Texas Instruments, etc). This will make possible a reduction of installation and commissioning costs and speed up commercial production of the device. The project use of programmable logic integrated circuits produced by a concrete manufacturer will be determined at the stage of functional circuit development.

4. Development of signal processing and measuring system testing algorithms as well as engineering of requirements for the device behavior:

–Optimum wave lengths and numbers shall be selected to create devices that detect glycated hemoglobin in blood. Number of wavelengths determines number of optoelectronic sensor pairs.

–Algorithms and programs for signal filtering shall be developed. Signal filtering shall be performed at both hardware and software level.

–Circuits shall be tested and debugged; requirements for the coupling systems and interfaces ensuring simple-to-operate feature of the devices shall be specified.

5. Chip programming; development of a DM-sensor signal conversion module; error effect modeling:

–Programs for making LSI inter-element connections to create measuring and steering circuits shall be composed. An elemental base (FPGA, PLD, etc.) shall be finally selected.

–A conversion module to convert DM-sensor signal into glycated hemoglobin value shall be created. Sources and receivers of optical radiation in the form of chips will be installed in a device fixed to the patient’s body. Operation of the device which realizes optical method in vivo, is as follows. Optical radiation from a source is applied to a part of the body (fingertip, earlobe, etc.) using fiber-optic sensor. Reflected and/or passed-through optical signals are transmitted over optical fiber to a photodetector, wherein their analog and digital processing takes place by a spe-cial program using up-to-date methods and hardware. Resulting information is generated in digital and graphical form. The enlarged version of the device’s block diagram is illustrated herein. The device structure combines a optical sensor unit, signal processing and measuring error correction module, data storage and display module, control and timing unit, computer communication module and feed system. A special feature of the device structure is that there is a need to process data from sensors whose principle of operation and output signals are of different physical nature, which, in its turn, dictates a necessity to use complicated conversion and data processing systems.

–Preproduction in vitro testing of the devices shall be made and the results compared with the reference biochemical findings (200 blood samples).

–Effect of random and bias errors on measurement results shall be evaluated through comparison of hardware-based values with biochemical findings.

–A user-friendly display and character-generating system for measured values shall be developed. A data retention technique in case of deenergization shall be provided [7].

6. Development of printed circuit boards, enclosures and laboratory testing of measuring systems:

–An optimum radio components layout on PCB and connections between components shall be provided to reduce noise pickup over trace lines and ensure maximum heat sink.

–Breadboarding variants and prototyping of device housings shall be analyzed using current and up-to-date CAD software packages.

–Preproduction testing.

–A methodology for in vivo determination of glycated hemoglobin concentration shall be developed using the developed device.

–A check test run of prototypes under in vivo conditions shall be conducted and hardware-based results compared with those of biochemical analyses (300 patients).

–A report on comparability of techniques and their applicability in clinical conditions shall be prepared.

7. Complex hardware/software debugging:

–Combined hardware/software debugging according to test programs and device operation under actual operation conditions shall be carried out. If necessary, changes in the information-measuring systems and programs shall be made. and accuracy of measurements appraised. Electronic version of design documentation and recommendations on hardware-based measurement in compliance with medical requirements shall be drawn up.

–-Accuracy of measurements in the determination of glycated hemoglobin concentration shall be appraised with random and bias errors effect taken into account.

–Recommendations on measuring methods optimization shall be elaborated.

–Create a database to store the results obtained during examination of patients.

8. Medicobiologic expertise of devices and their complex debugging:

–Prototype testing in clinical conditions with the assistance of medical personnel shall be conducted folloed by analysis of the measuring results (500 patients).

–Based on the results obtained, the recommendations on prototype modernization shall be worked out.

–A User Manual shall be developed.

To obtain information about composition of blood, it is proposed to use optical (spectral) technique, which may fully implement all advantages of noninvasive methods. The study of interaction between optical mode radiation and live tissue provides for very valuable information about the subject of inquiry. Possibility to obtain both qualitative and quantitative information over a great number of samples makes this approach the most attractive in medical diagnostics and monitoring [6].

To single out information about arterial blood only and abstract from the whole number of interfering factors related to other tissues, it is proposed to use a sphygmic technique.

The commonness of the engineering approach at all stages of the project lies in the fact that a considerable part of operations performed by the device are shifted off to software. It is because of the wide use of software systems that construction of the device may be simplified and quantity of inter-element connectors minimized. It makes wiring and installation, as well as debugging much easier.

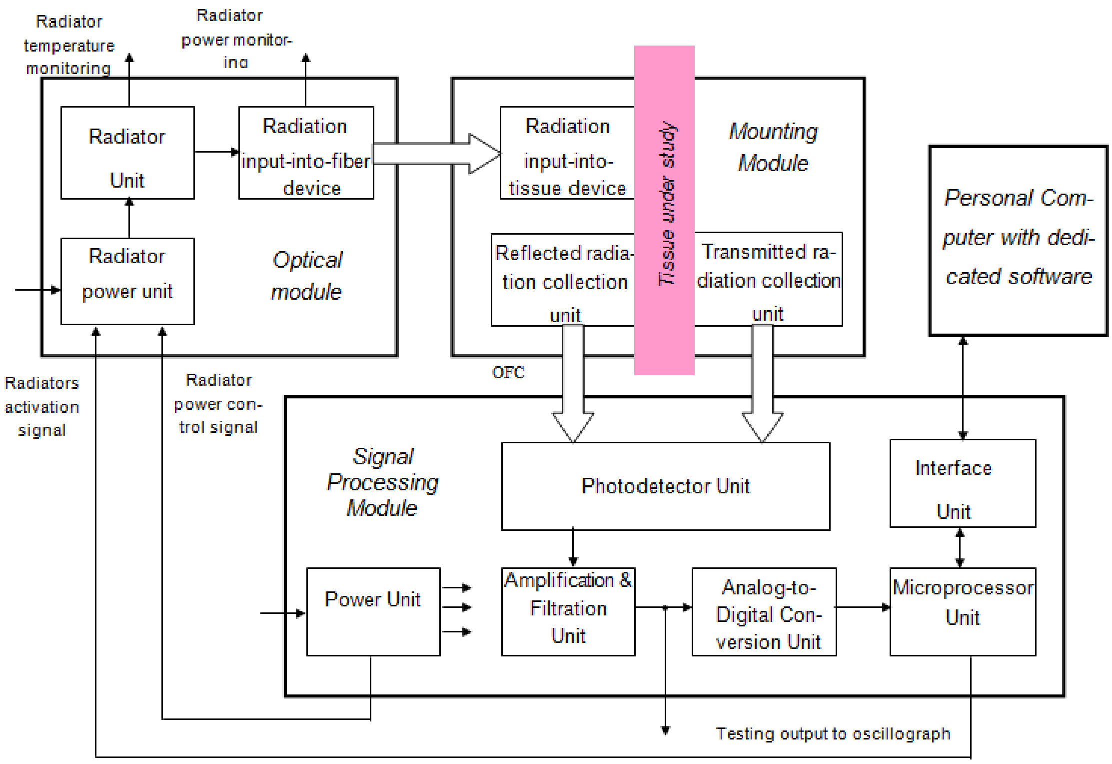

Figure 1. Block diagram of the device

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