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Principles of construction of hybrid microsystems for biomedical applications

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The paper analyzes the existing non-invasive methods and tools for measuring and monitoring heart rate (HR), glucose saturation and human blood glucose level (BGL), shows ways of improving them to increase accuracy and expand the number of parameters obtained by these methods, which became the basis for creating a hybrid microsystem device for biomedical applications.

A block diagram of the microsystem and a prototype of software and hardware tools for continuous monitoring of heart rate, BGL, saturation level and other blood parameters by photoplethysmography (PPG) have been developed. The proposed algorithms and tools provide primary processing of signals from optical sensors, calculation of pulse wave parameters, data transmission to mobile devices and a remote server, the possibility of calibration during operation based on research results.

Key words: sensory microsystem, non-invasive continuous monitoring, human blood glucose level, heart rate, saturation, absorption, mobile devices.

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Introduction

Currently, the rapid development of electronics and information technology leads to the emergence of new tools for clinical research and creates additional opportunities for remote monitoring of the patient's condition. However, for the study of blood parameters today, mainly invasive methods are used, accompanied by trauma to the patient, albeit slightly, the possibility of infection, as well as a rather long procedure for obtaining the result. The advantage of invasive methods compared to non-invasive methods is higher accuracy and reliability of the results. However, a significant number of publications [1-4] indicate that active research and implementation of non-invasive methods are underway, which allow continuous monitoring of heart rate, saturation, BGL and other parameters of patients, which sometimes, despite less accuracy, are more effective than classical invasive methods.

In particular, non-invasive methods of pulse oximetry have gained popularity, which are available on the market both in the form of portable and stationary medical devices for continuous saturation monitoring [5]. In [6], the physical principles of photometry were considered and the possibility of calculating the ratio of oxygenated and non-oxygenated fractions of hemoglobin in blood by absorption spectroscopy and elastic scattering spectroscopy was shown. The authors of [7] attempted to extend these methods to non-invasive monitoring of the level of bilirubin, hemoglobin and BGL, developed a prototype of a portable hemobiliglucometer device based on the method of analyzing optical light absorption and frequency separation using interference filters. However, the use of only one wavelength of 940 nm for determining BGL did not allow achieving the required accuracy, since at this wavelength the absorption coefficients of water and glucose are almost the same.

Other non-invasive methods are also used, in particular, in [8], the relationship between changes in the dielectric constant of blood due to changes in BGL and changes in the resonant frequency characteristic of electromagnetic radiation was shown, and an attempt was made to create a non-invasive glucometer based on a microwave resonator sensor, but the low noise immunity of the method and the need for further research were indicated.

In general, the analysis of literature and the state of the problem has shown the relevance of this topic and the need for further scientific and applied research to improve non-invasive methods and tools for measuring and monitoring heart rate, saturation and BGL.

I. Analysis of optical methods for non-invasive monitoring of blood parameters

Unfortunately, careful control of blood parameters, in particular BGL, is difficult to achieve with the current invasive technology, which involves puncturing the skin (most often a finger) to obtain a drop of blood. This method is inconvenient and painful, requires careful cleaning of the skin of the finger and is not suitable for frequent use. There is a need for a non-invasive sensor that allows frequent or continuous measurement of blood parameters, in particular BGL. Obviously, methods based on the analysis of light radiation will be useful, since they do not harm the body at negligibly low radiation energy and do not require chemical reagents, test strips, and other consumables.

One of the most common non-invasive methods is PPG, which consists in recording changes in the light intensity that occur when small vessels are filled with blood, depending on the phase of the cardiac cycle, by transilluminating a tissue area, for example, a finger, earlobe, tissue between the thumb and forefinger [9]. The intensity of the light transmitted through the tissue is proportional to the change in the blood supply to the tissue under study during contraction and relaxation of the heart muscle, i.e. determined by vessel size/volume of blood in the area of interest (Fig. 1). With the contraction of the left ventricle, a wave appears, the speed of which depends on the elasticity and thickness of the vascular wall, the width of the lumen of the vessel and the force of cardiac contraction.

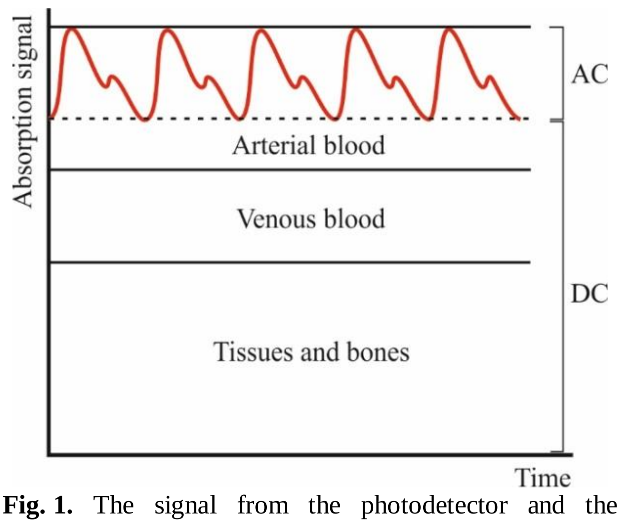

Fig. 1. The signal from the photodetector and the approximate distribution of the absorption of light radiation when passing through the body tissue.

The ratio of the variable component to the constant component makes it possible to determine the perfusion index, which depends on the intensity of blood flow at the measurement site, on the filling of the vessels, and the number of working capillaries. This parameter shows how ready the environment and the patient's body are for a correct measurement. The perfusion index (pulse modulation) values range from 0.3 to 20%. This indicator is individual for everyone and varies depending on the measurement site and the physical condition of the patient. A very low value of this parameter (less than 4%) can distort the measurement results and indicates, for example, hypothermia of the finger, the presence of vascular diseases.

The photoplethysmogram obtained after amplification and processing of the photodetector signal (Fig. 2) characterizes the state of blood flow at the sensor site.

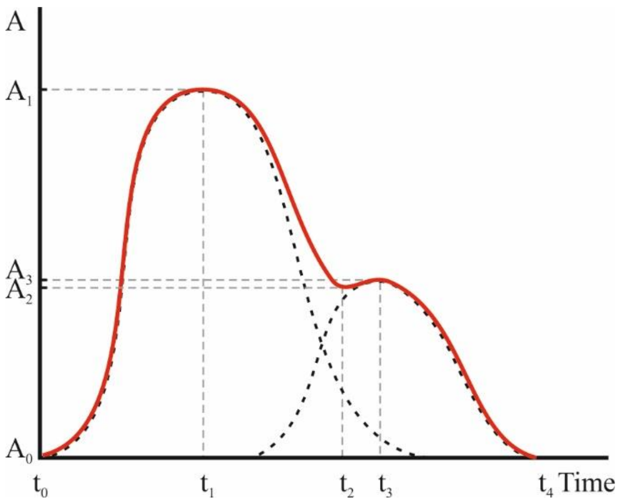

Fig. 2. Photoplethysmogram, schematically reflecting the pulse wave, the amplitude A_1 corresponds to the anacrotic period, the amplitude A_2 corresponds to the dicrotic period.

The first peak of the curve corresponds to the anacrotic period of the pulse wave, that is, the phase of the greatest contraction of the heart muscle, which is formed during the systole period. The magnitude of the pulse wave amplitude corresponds to the stroke volume of blood during cardiac output, which provides indirect information about the level of the inotropic effect. The second peak of the pulse wave, corresponding to the dicrotic period of the pulse wave, is formed due to the fact that when the blood is ejected by the heart under the action of increased pressure, elastic stretching of the aorta and large main arteries occurs, and when the systolic pressure decreases, they return to their original state, while ejecting the accumulated volume of blood. This peak corresponds to the diastolic period of the cardiac cycle and provides information about vascular tone. The top of the pulse wave corresponds to the largest volume of blood, and its minimum corresponds to the smallest volume of blood in the tissue area under study. It is believed that the frequency and duration of the pulse wave depend on the characteristics of the heart, and the magnitude and shape of the peaks depend on the state of the vascular walls.

The amplitude characteristics of PPG are relative, but their analysis in dynamics provides information on the magnitude of the vascular response. Time characteristics of the pulse wave provide information about the duration of the cardiac cycle, the ratio and duration of systole and diastole. These parameters have absolute values and can be compared with existing normative indicators. In particular, the time parameters studied are the duration of the anacrotic phase of the pulse wave, the duration of the dicrotic phase of the pulse wave, the duration of the pulse wave, the ascending wave index (a parameter that reflects the filling phase in the systolic period of the cardiac cycle and corresponds to the ratio of the duration of the ascending segment of the anacrotic wave to the total duration of the pulse wave), the filling time (corresponding to the interval from the beginning of the pulse wave to the top of the anacrotic wave), the duration of the systolic phase of the cardiac cycle, the duration of the diastolic phase of the cardiac cycle, the reflection time of the pulse wave (corresponding to the relaxation time of the myocardium in the protodiastolic phase), heart rate.

The PPG method underlies many spectral methods of non-invasive blood analysis to determine the level of saturation, glucose, hemoglobin, bilirubin. Spectral methods are based on the dependence of the absorption capacity of some blood components on the wavelength of light.

Fig. 3 shows the absorption spectra of the main blood components, which can be used to determine the optimal absorption wavelengths for each of the analyzed blood components.

The absorption of light at a certain wavelength obeys the exponential Lambert-Beer law:

$$I = I_0 e^{-kCd}, \tag{1}$$

here I_0 and I are the light intensities before and after passing through the object of study (for example, through the earlobe or a finger), k is the coefficient corresponding to the absorption capacity of the object, C is the concentration of glucose in human blood, d is the thickness of the biological object.

To improve the accuracy of determining saturation or the level of glucose in the blood by the PPG method, the light absorption signals are normalized, for which the constant component at the moments of diastole A_{DC} and the ratio of the amplitudes of the pulsating A_{AC} and constant components A_{DC} are determined:

$$A_n = ln(A_{AC}/A_{DC}). \tag{2}$$

The normalization procedure is performed for each wavelength. The normalized absorption value does not depend on the intensity of the LED radiation but is determined only by the optical properties of the living

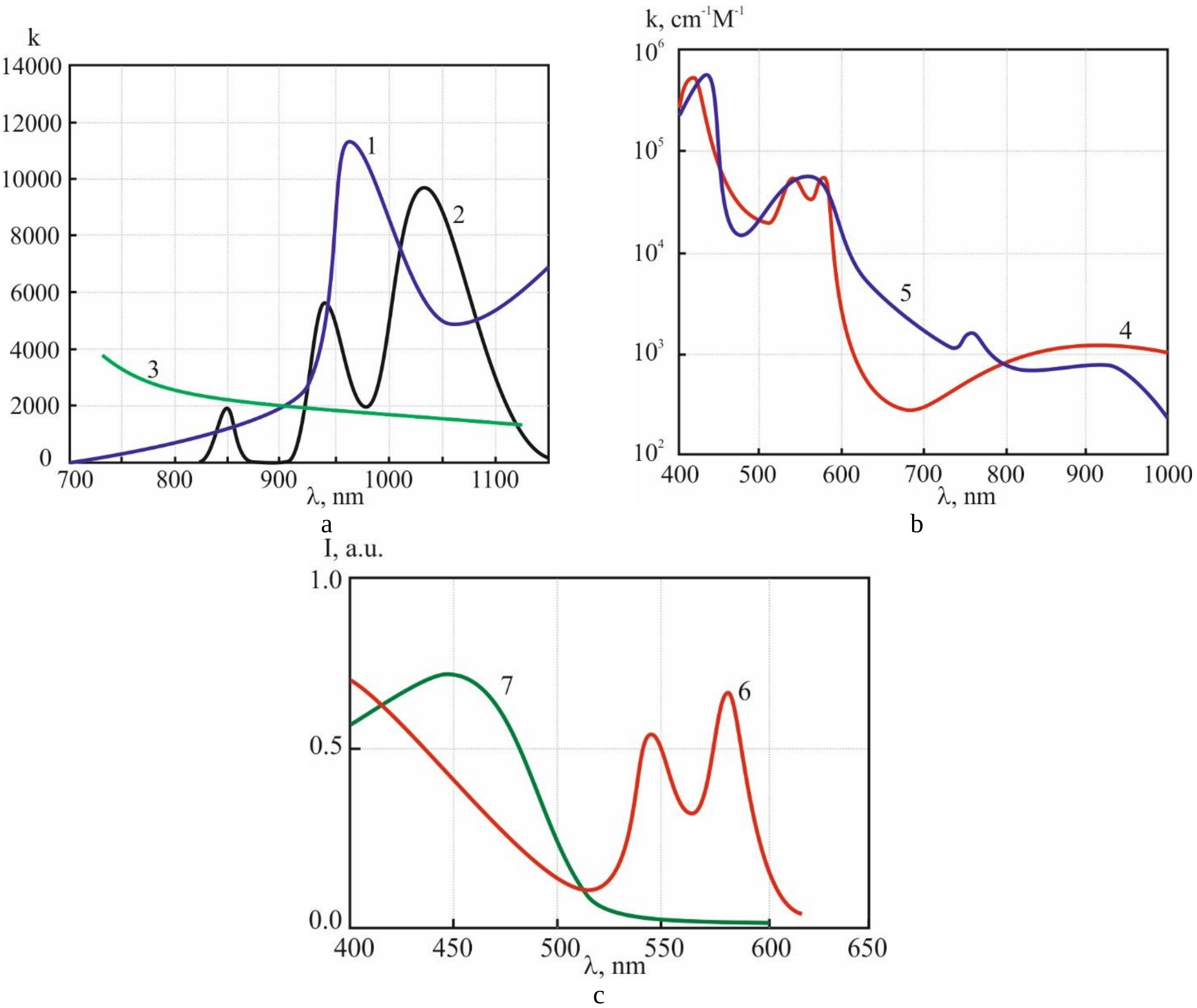

Fig. 3. Absorption spectra: water (1), glucose (2), melanin (3) (figure a [10]), oxyhemoglobin (4), deoxyhemoglobin (5) (figure b [6]), hemoglobin (6) and bilirubin (7) (figure c [7]).

tissue.

To obtain saturation values, glucose levels, hemoglobin or bilirubin values, the ratio of normalized light absorption values for two selected wavelengths is calculated:

$$R = A_{n1}/A_{n2}. \quad (3)$$

To improve accuracy, a combination of more than two wavelengths can be used, for example, for glucose, the characteristic wavelengths 840, 940, 1045 nm in relation to the reference wavelength will give three coefficients R_1, R_2, R_3.

The value of R is empirically related to the values of the measured value by the calibration dependence obtained in the process of instrument calibration.

The main still unresolved problem is the distinction between the influence of individual blood components due to the large number of overlapping absorption spectra for some components, as well as the influence of other factors such as body temperature, perfusion index, instrument drift, environmental conditions. In particular, the concentration of glucose in the blood is rather insignificant and its determination by optical methods is significantly affected by changes in the concentration of other components, for example, a change in the concentration of oxyhemoglobin, since clinically significant fluctuations in BGL cause very small spectral changes. Clinically accurate readings require a signal-to-noise ratio of around 10^5, which results in high performance requirements for any spectroscopic instrument.

At first glance, it seems more advantageous to measure BGL in the mid-IR range due to the weaker signal in the near-IR range. But since water, which is the main component of blood and tissues, has a significant absorbing power in the entire mid-IR region, light in this range can only penetrate less than a few hundred micrometers, which makes it impractical for non-invasive measurements in vivo.

To separate the influence of individual blood components, attempts are being made to use additional physical phenomena, in particular, the property of glucose to rotate the plane of polarization of linearly polarized light. The amount of rotation is a linear function of the path length, the concentration of the components, and the specific rotation constant. At physiological concentrations and a path length of about 1 cm, the rotation of the plane of polarization due to glucose is about 5 millidegrees [11], which, in combination with the scattering and depolarizing properties of the skin, makes it practically impossible to use this measurement method transdermally. However, the use of a rotating polarizer will make it possible to obtain a variable periodic signal, the phase of which will carry information about the angle of rotation of the polarization plane caused by the presence of glucose, which will increase the accuracy of PPG method.

Another method that can complement the PPG method is photoacoustic spectroscopy, which is based on the detection of ultrasonic vibrations emanating from a substance under the action of laser radiation and capable of providing a higher sensitivity than conventional spectroscopy. Unfortunately, this method of glucometry is quite expensive and most sensitive to environmental conditions. There is also the problem of finding a way to maintain a low skin surface moisture content at the measurement site.

A significant increase in accuracy can be achieved using modern software data processing capabilities, in particular, adjusting the calibration curve during operation for a specific user by implementing a database with the possibility of periodically entering data from non-invasive and laboratory studies and calculating correction factors.

Photometric methods are well combined with other methods, for example, with methods of cardiography, which makes it possible to determine blood pressure due to its relationship with the speed of the pulse wave [12-13].

II. Software and hardware design

The design of software and hardware is represented by a number of stages, each of which solves specific tasks for the development of non-invasive monitoring of blood parameters. In particular, this is the choice of optimal frequencies and a combination of light sources, filters and photodetectors, the development of filtering and data preprocessing algorithms, the development of software with the ability to input data obtained by other methods and algorithms for automatic correction of calibration curves.

The frequencies were chosen in such a way as to obtain the maximum difference in the absorption coefficients for a particular blood component, and the frequencies (wavelengths) at which the absorption coefficients are close and minimal were used as reference frequencies (reference wavelengths).

For glucose, the wavelengths can be determined from Fig. 3a: the first is in the region of almost complete transparency of glucose and almost the same absorption of water and melanin – 880-900 nm, the second is in the region of almost the same absorption of glucose and water – 940 nm, the third is in the region of the peak of water absorption and minimum absorption of glucose – 970-980 nm, and the fourth is in the region of the peak absorption of glucose and the minimum absorption of water and melanin – 1030-1045 nm.

The choice of optimal wavelengths for determining saturation was made by analyzing the absorption spectrum of oxyhemoglobin and deoxyhemoglobin (Fig. 3b): the first wavelength is in the region of the minimum absorption of oxyhemoglobin – 630-670 nm, the second wavelength is in the region of maximum absorption of oxyhemoglobin and minimum absorption of deoxyhemoglobin – about 940 nm, the third reference wavelength is at the intersection of the absorption curves – 780-800 nm.

The optimal wavelengths for determining the total level of hemoglobin and bilirubin will be 540-580 nm, since the maximum absorption of hemoglobin (Fig. 3, b, c) and the maximum absorption of bilirubin are 450-460 nm. Also, the wavelength of maximum absorption of hemoglobin 540-580 nm is well suited for studying the amplitude-time parameters of the pulse wave, since the variable component of the signal will be maximum.

Therefore, to implement a sufficiently versatile device, the simultaneous use of 5-7 frequencies of optical radiation is required, and two options for implementing the device are promising. The first and most widely used method of pulse oximetry is the use of miniature LEDs or laser diodes at selected frequencies and a single broadband receiver. The advantages of this implementation are the simplicity of the optical system and the absence of the need for expensive narrow-band filters for the required frequencies when choosing narrow-band sources of optical radiation, high sampling rate and low power consumption. The disadvantages are the significant dimensions of the light sources, the problem of availability of narrow-band LEDs or laser diodes at certain frequencies.

The second implementation option is to use a single light source with a wide and most uniform spectrum, an optical system for the formation and direction of the light beam and a line of photodetectors, in front of which interference bandpass filters are installed at the required frequencies. A tungsten halogen or ordinary miniature incandescent lamp with a wide spectrum can act as such a source (Fig. 4). By setting the lamp supply current, it is possible to obtain the required spectral characteristics, and with a sufficiently narrow spiral, the sampling frequency necessary for the pulse wave analysis.

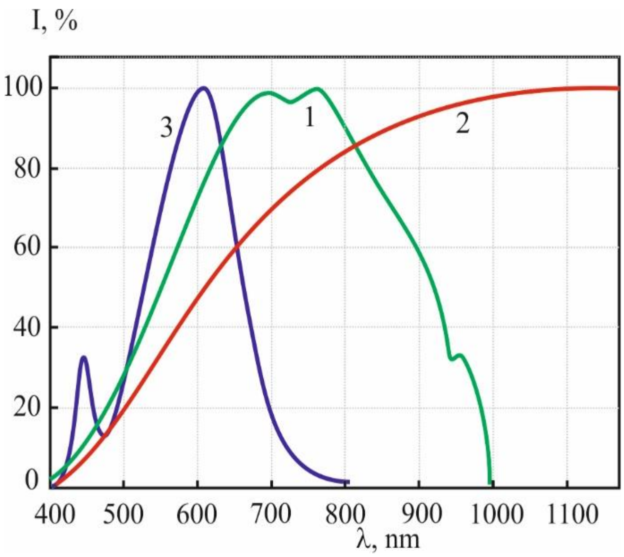

Fig. 4. Emission spectrum of an incandescent lamp (1), a halogen lamp (2) and a white LED (3).

The advantage of such a system is the possibility of miniaturization due to the implementation of the photodetector and filters in an integrated design, which will provide more accurate selection of the necessary frequencies by narrow-band filters and reduce the spread of parameters, noise, and interference due to the integrated design. A significant disadvantage is the high power consumption of the incandescent lamp, the complexity and high cost of manufacturing technologies for optical systems and sensors.

To assess the possibilities and working out algorithms for processing signals from the photodetector, the first method of designing a prototype was chosen using several narrow-band light sources and one broadband photodetector. A high-precision miniature light sensor with an I2C VEML6030 interface (Vishay Semiconductors, USA), which has an almost uniform sensitivity in the range of 400-800 nm, which gradually decreases, but still allows measurements up to wavelength of 900 nm, is well suited as a broadband receiver. But this sensor has a low measurement frequency of 10 Hz, which is not enough for a complete analysis of the amplitude-time parameters of the pulse wave. So, BH1680FVC (Rohm Semiconductor, Japan) and OPT101 (Texas Instruments Incorporated, USA) with built-in transimpedance amplifier are used as the main high-frequency photodiodes, and a BPW34 infrared photodiode (OSRAM, Germany) is used to extend the range and equalize the sensitivity in the infrared region of the spectrum. The use of several sensors simultaneously, the spectral sensitivity of which is shown in Fig. 5, provides high and almost uniform spectral sensitivity over the entire operating wavelength range of 450-1050 nm and a high sampling rate to enhance filtering and signal processing capabilities to accurately determine the time parameters of the pulse wave. Also, the use of several photodetectors makes it possible to place them more accurately in front of the corresponding light source. It is also possible to use universal photodetectors with several RGB channels and an infrared channel in one housing, for example TMD37003M (AMS, Austria).

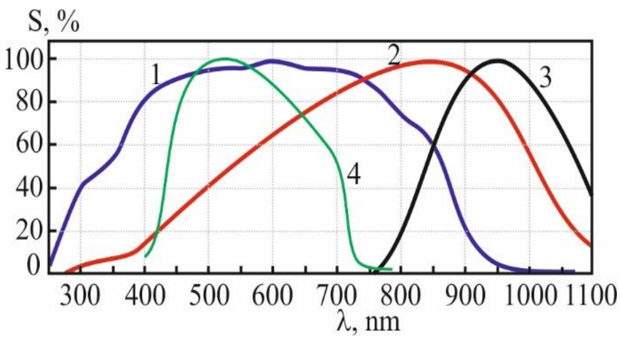

Fig. 5. Spectral sensitivity of photodetectors: VEML6030 (1), OPT101 (2), BPW34 (3), TMD37003M (4).

As light sources, LEDs from Foryard Optoelectronics, Vishay Semiconductors, OptoSupply were used, which are available at all main wavelengths, except for wavelengths above 950 nm, and from AMS Osram – 1050 nm. The advantage of using LEDs is low cost and miniature SMD housings with sufficient radiation intensity. The disadvantage is the relatively wide emission band. At some wavelengths, in particular, 650, 780, 905, 940 nm, laser diodes are available that have a much narrower emission band, but also significant dimensions.

The general block diagram of the developed hybrid sensor microsystem for biomedical applications is shown in Fig. 6.

STM32WB (STMicroelectronics) was chosen as a control microcontroller, which combines a low-power Cortex-M4 core and a Bluetooth Low Energy 5.2 wireless interface in a small housing. This will reduce the size of the device and maximize battery life, which is important in a compact design in the form of an ear clip for continuous monitoring. When the device is made in the classical form of a clamp on a finger, we have significantly

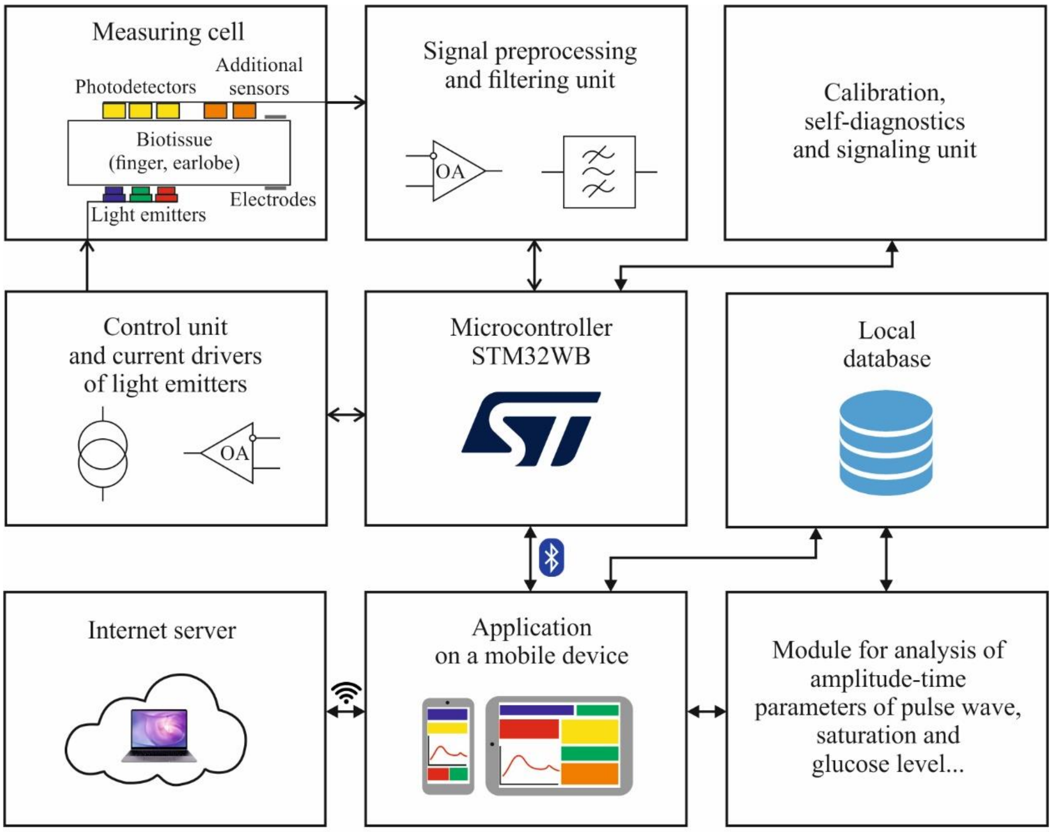

Fig. 6. Block diagram of a hybrid sensor system for biomedical applications.

lower requirements for miniaturization, but such devices are not convenient for continuous monitoring, although this design is optimal for prototyping. Also, these microcontrollers have advanced peripherals, in particular, a 10-channel 12-bit ADC with the possibility of differential measurements, hardware USB and built-in hardware security and encryption functions.

The human heart rate ranges from 60 to 180 beats per minute. Therefore, the filter is designed to pass frequencies from 0.5 to 10 Hz, which eliminates power frequency noise, high frequency noise and low frequency drift. The pulse wave signal from the photodetectors, previously amplified and filtered by a hardware filter, is digitized by the ADC of the microcontroller at a frequency of 200 counts per second for each channel and stored in the array. The data can be both transmitted via Bluetooth and processed by a microcontroller to determine the parameters of the pulse wave, saturation and glucose level, which is necessary for signaling and monitoring, in particular, in the absence of communication with a mobile device. This allows the user to connect the mobile device only while using the application or periodically to transfer data to the server, which significantly saves battery power. As a power source in the case of an earlobe clip, it is convenient to use miniature lithium-ion batteries of the LIR2032 type, it is also possible to use smaller batteries, for example LIR1220, and thin-film thermoelectric converters based on IV-VI compounds to extend the period of operation without recharging [14-17], which can work due to the temperature difference between the human body and the environment.

Fig. 7 shows typical curves of the pulse wave signal after amplification and filtering, obtained for different frequencies of optical radiation, from which the parameters of the pulse wave are determined.

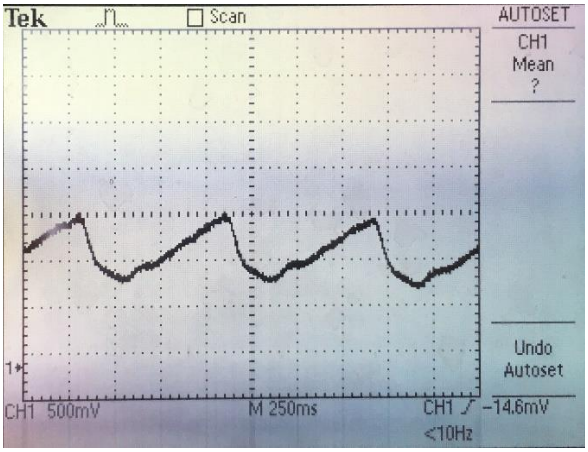

Fig. 7. Oscillogram of the pulse wave signal.

The pulse wave analysis algorithm consists in processing an array of digitized data, determining the points A_0-A_3 and T_0-T_4 (Fig. 2), which allow you to determine the heart rate, the ratio and duration of systole and diastole, the duration of the pulse wave, the ascending wave index, the filling time, the pulse wave reflection time, etc. Also, from the value of A_n calculated by formula (2), the perfusion index is determined, based on which the self-diagnosis unit concludes how the device, the environment, and the user's body are ready for the correct measurement, excluding incorrect data from entering the database. Then, for pairs of frequencies corresponding to a specific blood component, the corresponding coefficients R_n are calculated using formula (3). Based on the obtained values of R_n and the empirical calibration curves stored in the memory of the device, the levels of saturation, glucose and bilirubin in the blood are obtained. The database is used both for long-term storage of measurement data with the possibility of uploading them to a remote server, and for entering data obtained by more accurate methods, in particular laboratory and using certified invasive glucometers, with real-time reference. This allows corrections to be made to empirical calibration curves in the device memory, thereby improving accuracy and adapting the device to the characteristics of the body of a particular user. The mobile application provides a convenient interface when working with both local and remote data and a long battery life of the device in continuous monitoring mode thanks to the ultra-low consumption BLE 5.2 data exchange protocol, and the alarm module will report when the parameters go beyond the set limits, even if the application on the mobile device is not running.

III. Discussion of the results and prospects for the development of the method

In general, the PPG method and the hybrid microsystem prototype developed on its basis showed good results. As can be seen from Fig. 8, a sufficiently clear and stable signal was achieved, from which it was possible to accurately determine the parameters of the pulse wave. The implemented PPG method allows non-invasively and promptly obtaining information about the work of the heart, changes in blood circulation parameters under the influence of various physical factors, which is important, for example, in physiotherapy and sports, the treatment of many diseases, and can also become one of the options for solving the problem of fast, high-quality and the same time available diagnostics and monitoring of blood circulation. An analysis of optical radiation at wavelengths of 570, 630, and 940 nm made it possible to determine the parameters of the pulse wave and blood oxygen saturation with an accuracy no worse than portable and stationary commercial pulse oximeters. The determination of bilirubin in the framework of this work was not carried out. The use of two electrodes inside the clamp and one electrode outside the housing allows measuring the impedance and electrical impulses of the cardiogram of the heart (it is necessary to touch the outer electrode with the other hand). This makes it possible to determine the propagation velocity of the pulse wave and blood pressure by superimposing the electrical signals of the heart and the signals from the optical sensor according to the method described in [12, 13]. To determine the level of glucose, only LEDs at wavelengths of 850, 890, 940 nm are widely available. At these wavelengths, the absorption of glucose, water, and melanin is quite close (Fig. 3, a), and the accuracy of determining the glucose level is significantly inferior to classical invasive glucometers. There are also quite expensive LEDs at wavelengths of 1020 nm and 1050 nm, close to the glucose absorption peak at 1035–1040 nm (Fig. 3, a). The availability of narrow-band sources for all necessary wavelengths would significantly increase the accuracy of blood glucose measurement by this method.

Another option is possible using a broadband source. A miniature tungsten halogen incandescent lamp (Fig. 4) can be used as a source of all the required frequencies, but then appropriate narrow-band filters are required to select the necessary frequencies. For some combinations of frequencies, there are integrated sensors that are commercially available, such as the TMD3700 (AMS, Austria), but the list of available frequencies is very limited, and the filter bandwidth is too wide for this application. The idea, which is under further study, is to develop an integrated light receiver that will contain several photosensitive sensors on a single chip, and the required frequency will be allocated by narrow-band optical interference film filters deposited on the surface of the sensors. In addition, it is planned to implement on-chip operational amplifiers and adjustable band-pass filters for electrical signals, a temperature sensor [18], and a temperature drift compensation circuit.

Conclusions

The existing principles and methods of non-invasive measurement and monitoring of heart rate, blood oxygen saturation, BGL have been analyzed, ways of their improvement have been shown to increase the accuracy and expand the number of parameters obtained by these methods.

A block diagram of the microsystem, algorithms, and a prototype of software and hardware tools have been developed that provide preprocessing of signals from optical sensors, calculation of pulse wave parameters, data transmission to mobile devices and a remote server, and the possibility of calibration during operation for continuous monitoring of heart rate, the saturation level, BGL, and other blood parameters using the PPG method.

It has been found that the use of wavelengths up to 940 nm is insufficient for a clinically used measurement of BGL. Methods for increasing the accuracy by expanding the wavelength range to 1045 nm with a broadband emitter have been proposed, and the wavelength selection is carried out by interference filters introduced in front of photodetectors in an integrated or hybrid design.

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Принципи побудови гібридних мікросистем для біомедичних застосувань

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В роботі проаналізовано існуючі неінвазивні методи та засоби вимірювання та моніторингу частоти серцевих скорочень (ЧСС), сатурації та рівня глюкози в крові людини (РГКЛ), показано шляхи їх вдосконалення для підвищення точності та розширення кількості отримуваних параметрів цими методами, що стало основою для створення пристрою гібридної мікросистеми для біомедичних застосувань.

Розроблено структурну схему мікросистеми та прототип програмно-апаратних засобів для неперервного моніторингу серцевого ритму, показників РГКЛ, рівня сатурації та інших параметрів крові методом фотоплетизмографії (ФПГ). Запропоновані алгоритми та засоби забезпечують первинну обробку сигналів від оптичних сенсорів, обчислення параметрів пульсової хвилі, передачу даних на мобільні пристрої та віддалений сервер, можливість калібрування в процесі експлуатації на основі результатів досліджень.

Ключові слова: сенсорна мікросистема, неінвазивний неперервний моніторинг, рівень глюкози в крові людини, серцевий ритм, сатурація, поглинання, мобільні пристрої.