Wireless dynamic light scattering sensors detect microvascular changes associated with ageing and diabetes.

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***Abstract*— This paper presents clinical results of wireless portable dynamic light scattering sensors that implement laser Doppler flowmetry signal processing. It has been verified that the technology can detect microvascular changes associated with diabetes and ageing in volunteers. Studies were conducted primarily on wrist skin. Wavelet continuous spectrum calculation was used to analyse the obtained time series of blood perfusion recordings with respect to the main physiological frequency ranges of vasomotions. In patients with type 2 diabetes, the area under the continuous wavelet spectrum in the endothelial, neurogenic, myogenic, and cardio frequency ranges showed significant diagnostic value for the identification of microvascular changes. Aside from spectral analysis, autocorrelation parameters were also calculated for microcirculatory blood flow oscillations. The groups of elderly volunteers and patients with type 2 diabetes showed a statistically significant decrease of the normalised autocorrelation function in time scales up to 10 s. A set of identified parameters was used to test machine learning algorithms to classify the studied groups of young controls, elderly controls, and diabetic patients. Our conclusion describes and discusses the classification metrics that were found to be most effective.**

***Index Terms*— Laser Doppler flowmetry, blood perfusion, wireless sensor, VCSEL, diabetes mellitus, autocorrelation, wavelet transform, machine learning.**

I. Introduction

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The demand for wearable electronics devices has steadily increased over the past decade. With the rise of smartphones and their penetration into everyday life, wearable devices have become tools that extend their functionality. Most wearable electronics are used to alert by communicating with a smartphone, to monitor physiological signals and motion activity, to detect ambient temperatures and to deliver drugs. The recent impressive rise of such wearable medical technologies can be explained by the widespread distribution of smart devices, the growing popularity of smart watches and fitness bracelets against the background of increasing public concern for health and quality of life, together with the increase in lifestyle diseases and an ageing population. The rapid surge in lifestyle diseases and increased treatment costs are encouraging people to take a more thorough approach to their health care and prevention of diseases. Therefore, monitoring physiological and biophysical parameters by means of wearable diagnostic devices is becoming more and more relevant.

Due to their small external dimensions and use of wireless communication technologies, wearable medical devices are portable and suitable for daily use. Wearable sensors have opened up qualitatively new possibilities for diagnosing human health conditions, e.g., the monitoring of human physiological parameters in natural conditions in real time. The growing energy efficiency of electronic components reduces the necessity for massive battery modules and allows daily monitoring.

The skin is the largest organ of the human body and is responsible for many physiological functions. The skin not only acts as a primary layer of defence against injury, but it also provides tactile sensitivity, the sensation of temperature, vibration, pressure, and fortunately for us, has a cellular makeup that, when analysed, can give viable data on a host of human functions. Systemic abnormalities at the level of the microcirculatory bed (blood microcirculation and regulatory mechanisms) play a crucial role in the pathogenesis of rheumatic and cardiovascular diseases [1] and diabetes [2], and are also markers of cancer and various skin diseases [3]. Thus, daily monitoring of these parameters in the skin is vital for assessing the general condition and for detecting the onset of pathological changes that are reversible with timely diagnosis and treatment.

Against the background of a current surge of interest in wearable electronic diagnostic devices, the application of long

practised and well-known technologies in a compact format that is convenient for everyday use becomes a new area of research. One of these technologies that has outstanding potential in assessing peripheral blood flow is laser Doppler flowmetry (LDF) [4]. Since the early 1990's, LDF measurements have become an object of wide research and industrial interest in the field of life sciences. At present, there is an assortment of devices for in-vivo measurements using laser Doppler flowmetry. LDF imagers (including laser speckle imagers) and LDF monitors are two main types which are commercially available. These systems allow measurements in one point of living tissue (monitors) or visualisation of the blood flow in the microcapillaries of the skin and living tissues (imagers) at a depth of 1-2 mm. These LDF imagers are considered to provide highly reliable diagnostic results. However, in most cases, they are stationary, stand-based devices, which see application in diagnosis of different skin injuries (burns, nonhealing wounds, etc.) within medical centres. Examples of such systems are: PeriCam PSI^{TM} (Perimed AB, Sweden) [5], moorLDI2^{TM}, moorFLPI^{TM} (Moor Instruments, UK) [6], [7].

On the other hand, in general, LDF monitors suffer from a lack of repeatability in their measurements [8]. The sampling volume of the probes approximates to 1 mm^3. Thus, the position of the probe placement has a crucial impact on the registered signal, due to the high spatial heterogeneity of the microvasculature of the skin and living tissues. Examples of such systems are: PeriFlux System 5000^{TM} (Perimed AB, Sweden) [9], moorVMS-LDF^{TM} (Moor Instruments, UK) [10].

The appearance in the market of ultracompact, semiconductor, power-efficient lasers makes it possible to build new, compact, dynamic light-scattering sensors implementing the laser Doppler flowmetry signal processing approach for wearable electronics. The wearable implementation of LDF can become a truly new diagnostic interface to monitor the heart and cardiovascular system, which could be of the greatest interest for the prediction of CVD [11], as well as in sports and rehabilitation medicine. Such new features cannot be provided by conventional LDF monitors and imagers, due to the short record duration and fragmentary nature of the measurements. A fine analysis of capillary blood flow structure and rhythm in the time and frequency domains, coupled with a new possibility of round-the-clock monitoring, can provide valuable diagnostic information about stressful conditions in the body, sleep quality, the effects of smoking, alcohol consumption and endothelial dysfunction, which is usually a herald of more severe CVD [12], [13]. The collection of these advantages presented in LDF systems introduced into a wearable format demonstrates that this technology has the potential to completely replace the pulse sensors based on light reflection currently present in all modern fitness bracelets and smart watches. There are several scientific groups researching this field [14], but compact diagnostic devices using LDF sensors are not yet available for monitoring major diseases such as cardiovascular conditions and complications related to Diabetes mellitus.

Diabetes mellitus (DM) is one of the greatest challenges of the 21st century, and its early diagnosis, care and treatment are among the highest priorities of the modern healthcare system. According to the International Diabetes Federation, there were almost 537 million people affected by the disease in 2021, and this number is expected to increase by almost 1.5 times over the next 30 years [15]. The presence and severity of chronic DM complications, resulting from prolonged exposure of the cardiovascular and nervous systems to high glucose concentrations, determines the length and quality of life of patients [16], [17]. Evidence shows that early diagnosis and timely treatment can prevent, slow down and in some cases even reverse the development of diabetic complications [18].

Laser Doppler flowmetry has been developed for the diagnosis of metabolic and perfusion complications associated with DM for more than 35 years; in fact, DM was one of the first areas of clinical use of LDF [19], [20]. In studies of diabetes complications, both single-point and image technologies were used. An important aspect of microcirculation research is the response to provocative stimuli, such as local skin heating and acetylcholine stimulation. Through the use of such effects, one can evaluate maximum vasodilation, which is significantly lower in diabetic patients than in healthy controls because of impaired microcirculation. Regardless of complications, patients with DM have impaired function of the endothelium [21] and reduced skin blood flow in response to local heating [22], local pressure [23], ionophoresis [24], and abnormal vasomotion [25].

This study aimed at the development and characterisation of novel wireless portable dynamic light scattering sensors that implement laser Doppler flowmetry signal processing for monitoring skin blood perfusion. In particular, the research focused on the possibility of detecting diabetic and ageing-related microvascular changes in the skin of the wrists.

II. Materials and Methods

A. Wearable Devices for Monitoring of Blood Perfusion

To register blood perfusion, a system of multi-channel wearable laser Doppler flowmeters "LAZMA PF" (LAZMA Ltd, Russia; in EU/UK this device is made by Aston Medical Technology Ltd., UK as "FED-1b") was used [26]. The system of capillary blood flow sensors consisted of one to four wearable devices containing a built-in LDF sensor, and wireless data acquisition module. Each wearable sensor in the system uses vertically emitting laser (VCSEL) as a single-mode laser source to realise direct tissue illumination without the use of optical fibre. The devices implement identical channels for recording blood perfusion and allow simultaneous measurements at multiple points in the body. The fibre-free solution and direct illumination of the fabric with a laser diode allows the device to avoid loss of adhesion to the fibre, as well as reduce the movement artefacts that are typical of fibre LDF monitors. By recording from different body areas within a time-synchronised manner, we can study the synchronisation of skin blood flows under different conditions [27], [28]. Fig. 1 exemplifies the structure of the implementation of the wireless portable devices used in this study for blood perfusion monitoring. .

Fig.2 illustrates the signal processing principle in these portable LDF devices. A single-mode VCSEL is supplied with

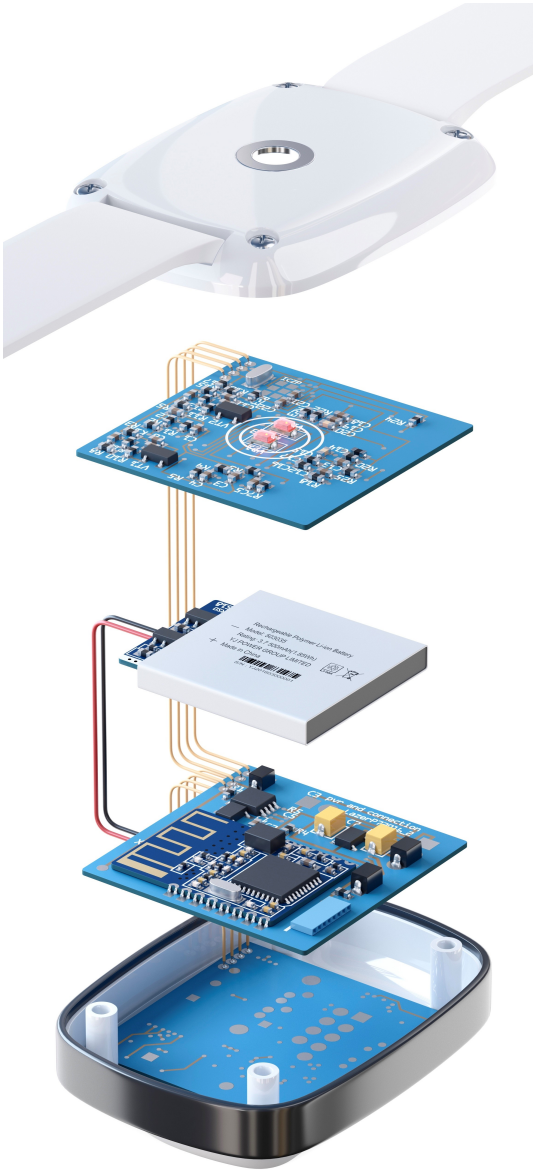

Fig. 1. Exemplary implementation of the wireless portable laser Doppler blood perfusion monitor.

current by the laser source driver. In the biological tissue, near-infrared laser radiation is partially scattered and partially reflected by moving red blood cells, accumulating Doppler shifts. The intensity of the light field on the surface of the skin is registered by photodiodes arranged symmetrically in a line, with the laser source in the centre. Due to the use of two identical measuring channels, the synphase component of the photocurrent can be reduced via the balanced detection principle. The photodiodes generate a photocurrent proportional to the incident radiation, which the current-voltage converter converts to a voltage. Next, the signal is transmitted to two parallel filters: a low-pass and a high-pass filter. An analogue-to-digital converter converts the filtered signal into digital form, which is then transmitted via Bluetooth to a device (personal computer or smartphone). With bespoke software, the operator controls the device (starting and stopping recording, setting the measurement timer).

The result of the perfusion measurement (in arbitrary perfusion units - p.u. [29]) using the wearable LDF device described above can be seen in Fig.3a. Figure 3b shows the amplitude-frequency spectrum of the signal obtained by its wavelet analysis. In general, the LDF signal recorded from the human skin has 5 oscillatory components in different frequency ranges with different physiological origins [30], [31]. These components represent endothelial, neurogenic, myogenic, respiratory and cardiac influence on microcirculatory blood flow and will be explained further in the paper.

Various reactivity tests are often used in studies with LDF, as their use allows a better assessment of microvascular function. The assessment of postocclusive reactive hyperaemia (PORH) in the occlusion test is one of the most frequently used tests. Fig.3c shows a typical example of perfusion recording during a brachial arterial occlusion test using a wearable LDF device. The data demonstrate good sensitivity of the wearable LDF sensor to changes in perfusion during PORH.

B. Validation of the Sampling Volume of the LDF measuring channel

To interpret the results of optical non-invasive diagnostics obtained *in vivo*, it is necessary to know the diagnostic volume and penetration depth of the probing radiation. This allows a more conscious analysis of the tissues and blood vessels involved in the formation of a diagnostic signal. This study used Monte Carlo simulation [32], [33] to simulate the sensitivity depth of the detector (diagnostic volume). Using this approach, photons and tissue structural components are described as interacting objects. The results of the simulation of the diagnostic volume of the LDF devices used in the study can be found in Fig.4. A probing radiation wavelength of 850 nm can reach 1.5 mm in the case when the distance between the source and detector of radiation (the so-called "measurement base", one of the factors most influencing the value of the diagnostic volume [34]) is 1000 μm. During the process of ageing and with the development of pathologies, the skin undergoes structural and functional changes that affect blood filling parameters and blood microcirculation dynamics. As the simulation results show, the wavelength of 850 nm is one of the most effective wavelengths for probing the deep vascular plexuses of the skin, since it propagates up to the layers of the reticular dermis when used. As a result, many vessels feeding the skin contribute to the signal.

C. Experimental Protocol

Laser Doppler flowmetry presents numerous advantages for blood microcirculation measurements in the skin, due to its almost universal applicability. However, despite all the advantages of the method, the high heterogeneity of the anatomy and physiology of the skin's capillary network imposes requirements for conducting single-point studies. In our studies, we were mainly focused on microcirculation in the homologous regions of the contralateral limbs. Experiments were conducted on the dorsum of the wrists. This area represents a nonglabrous (or hairless) skin type. The microcirculatory

system of nonglabrous skin is regulated by both sympathetic noradrenergic vasoconstrictor nerves and separate sympathetic cholinergic vasodilator nerves [35]. It contains only very few arteriolo-venular anastamoses and has primarily a nutritive function.

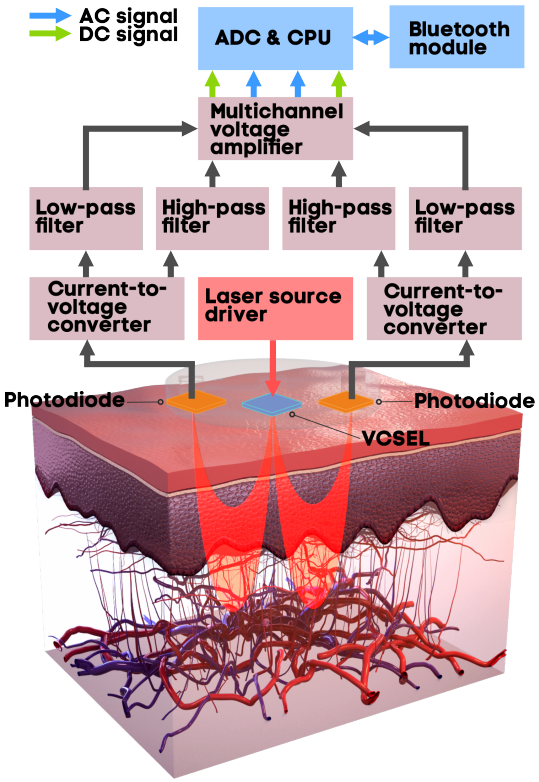

Fig. 2. Flowchart of the signal conversion in portable laser Doppler perfusion monitors.

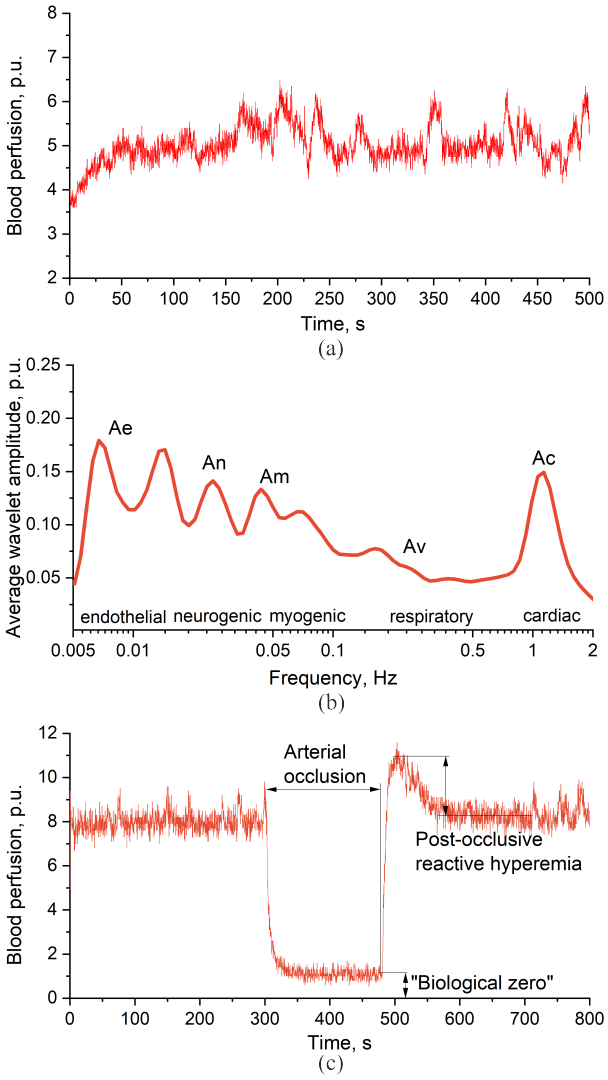

Fig. 3. Relevant examples of blood perfusion recordings during occlusion tests by portable LDF devices.

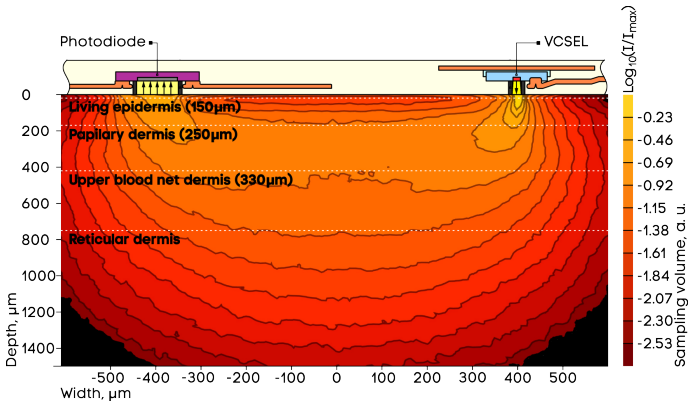

Fig. 4. Typical simulated sampling volume of the sensor.

The studies were conducted in accordance with the Helsinki Declaration of 2013 by the World Medical Association and approved by the Ethics committee of Orel State University (Protocol No. 15 of 21.02.2019). Study participants included 37 patients with diagnosed type 2 DM, 58 younger healthy volunteers (control group 1 - CG1) and 37 older controls (control group 2 - CG2: aged 46-70 years). Participants with cardiovascular disease and other serious diseases affecting the circulation system, as well as those with alcohol or drug dependence were excluded from the study. Table I shows the main clinical and laboratory parameters of the study groups. We recruited a younger control group to determine whether age and ageing affect the status of blood microcirculation, as the main group consisted of older individuals. The control group consisted of healthy volunteers with no cardiovascular or other serious chronic diseases that affect the circulatory system, and included healthy volunteers without cardiovascular or other serious chronic diseases. The main group included patients with diagnosed type 2 DM. The studies with patients was carried out on the basis of the Endocrinology Department of the Orel Regional Clinical Hospital (Orel, Russia).

In both control groups, volunteers had lower body mass indexes and blood pressures compared to the main group, as shown in the table I. Because obesity and hypertension are often associated with type 2 diabetes, avoiding this factor is difficult. Prior to the measurements, the volunteers filled out a questionnaire to identify health problems, which may affect the results of the study. Before the study, the subjects adapted

TABLE I
THE MAIN CHARACTERISTICS OF THE GROUPS UNDER STUDY

	CG1 n=58	CG2 n=37	DM n=37
Sex (M/F)	28/30	16/21	18/19
Age, years	22 ± 3	58 ± 12	60 ± 12
Body mass index, kg/m^2	22 ± 2	24 ± 4	32 ± 8
Systolic BP, $mmHg$	120 ± 8	123 ± 11	138 ± 17
Diastolic BP, $mmHg$	76 ± 8	76 ± 8	82 ± 9
Diabetes duration, years			13 ± 8
Fasting glucose, $mmol/l$			6 ± 2
HbA1c, %			9 ± 2
Total cholesterol, $mmol/l$			6 ± 2
Creatinine, $umol/l$			86 ± 21
Urea, $mmol/l$			6 ± 2
ALT, IU/L			29 ± 20
AST, IU/L			32 ± 17

to normal room conditions for 15-20 minutes. The volunteers were in a state of physical and mental rest. Experimental studies were conducted in the first half of the day, no earlier than 2 hours after a meal. The laser Doppler flowmetry devices were attached on the area of interest, without considerable pressure, a few minutes before the start of recording the signals. The devices were attached to the wrists just above the styloid process on the dorsal side of the arms. During the 15-minute measurement process, the subject was in a supine position. A total of 154, 78, and 78 blood perfusion recordings were obtained in the CG1, CG2, and DM groups, respectively, which were used in the analysis.

D. Data processing

In this study, we analysed the parameters of skin microcirculation oscillations, as well as the autocorrelation parameters of perfusion time series. In order to study the functioning of microcirculatory blood flow regulation systems, LDF signals $I_m(t)$ were subjected to wavelet analysis. MATLAB was used to carry out spectral analysis of signals using the complex-valued Morlet wavelet as an analysing wavelet [36]. The wavelet transform $W_x(f_{osc}, \tau)$ of a blood perfusion time-series $I_m(t)$ was defined in terms of the selected mother wavelet $\psi(t)$, as given in Eq. 1:

$$W_x(f_{osc}, \tau) = \sqrt{f_{osc}} \int_{\infty}^{\infty} I_m(t) \psi^*[f_{osc}(t-\tau)]dt, \quad (1)$$

where t is the time, τ is the time shift of the wavelet, f_{osc} is an estimate of the oscillation frequency ($\sim 1/a$, where a is the time-scale of the wavelet), and the symbol * indicates the operator of complex conjugation. A Morlet wavelet is defined as follows:

$$\psi(t) = e^{2\pi i t} e^{-t^2/2\sigma^2}. \quad (2)$$

Using this function, we can examine the amplitude and phase properties of oscillations of different frequencies in the analysing signal. The integrated wavelet spectrum was calculated by integrating Eq. (1) over period T of time-series recordings as follows:

$$M_{osc}(f_{osc}) = \frac{1}{T} \int_0^T |W_x(f_{osc}, \tau)|^2 d\tau. \quad (3)$$

In the LDF signal, wavelet analysis allowed the identification of five oscillatory components, located in different frequency ranges and corresponding to different physiological mechanisms that regulate blood flow. Blood flow oscillations were analysed at the following frequency ranges [30], [37]: 0.005–0.021 Hz (endothelial oscillations), both affected and unaffected by nitric oxide (NO); 0.021-0.052 Hz, which corresponds to the influence of neural innervation on blood flow (neurogenic oscillations); 0.052–0.145 Hz corresponding to smooth muscle activity (myogenic oscillations); 0.145–0.6 Hz representing respiratory movements (respiratory oscillations), and the 0.6–2 Hz range, which corresponds to the heartbeat (cardiac oscillations). By integrating the integrated wavelet spectrum (Eq. 3) in the frequency ranges mentioned, we were able to calculate the energy of the blood perfusion oscillations for every physiological mechanism. Compared with the metric based on calculating the maximum value of the integrated spectrum within a range of frequencies, this approach demonstrated better diagnostic value. We also calculated average perfusion for each recorded blood perfusion time-series. Consequently, each measurement taken from a volunteer was numerically characterised by a set of six parameters: five parameters of blood perfusion oscillations, and one parameter of average blood perfusion. Statistical analysis of the results was conducted using OriginPro software. The Mann-Whitney U-test was used to confirm the reliability of the differences. Statistical significance was determined by values of $p < 0.05$.

The final step of data processing involved testing the obtained feature space in a logistic regression classification model. Logistic regression is a simple and interpretable model for classification problems that can handle linear and non-linear decision boundaries, large datasets, and high dimensional feature spaces. We verified the quality of the binary classification for the pairs “young-older volunteers”, “young volunteers-diabetic patients”, and “older volunteers-diabetic patients”. Validation of the models consisted of randomly dividing the training set in proportions of 70% and 30%. The first part was used for model training, and the second part was used for validation. We repeated the procedure at least 30 times for each of the tested feature sets, allowing us to statistically estimate the main metrics for the implemented classification.

III. Results and Discussion

A. Time-series analysis

The correlation analysis (Fig. 6.a) shows that the groups of older volunteers and patients with type 2 diabetes demonstrate statistically significant decreases of the normalised autocorrelation function in time scales up to 10 s. Even so, the older

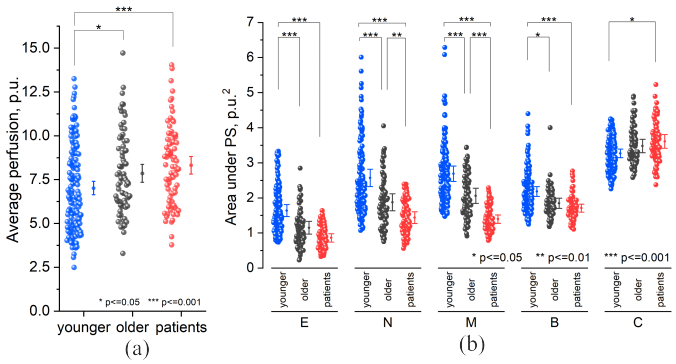

Fig. 5. Statistical analysis of average perfusion (A) and energy of blood perfusion oscillations (B) measured in wrists.

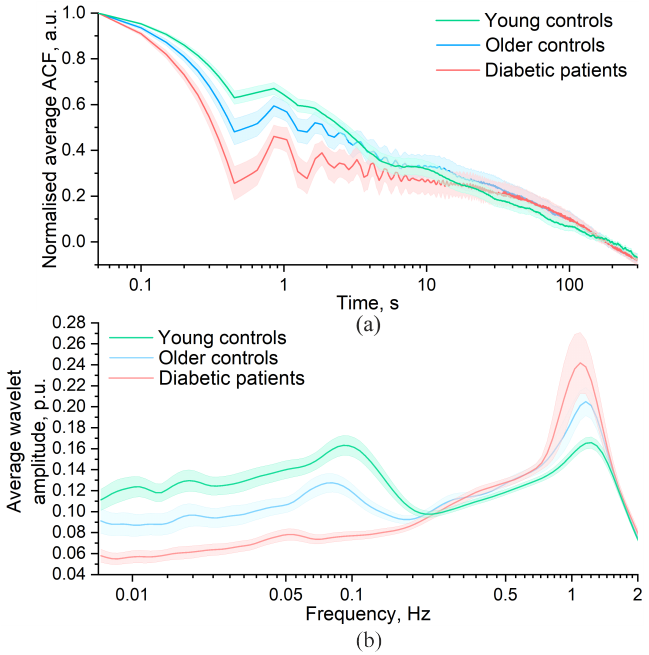

Fig. 6. Average plots of autocorrelation function (a) and wavelet amplitude spectra (b) of the blood flow recordings. A single SE is taken to show scattering.

controls still had higher values of the parameter compared to diabetic patients. Previously, the autocorrelation analysis of the blood perfusion time-series was applied to identify bifurcations in the skin blood flow affected by stroke [38]. Having higher levels of autocorrelation may be correlated with more regular mechanisms for controlling skin blood flow, which may have been substantially destroyed during the development of diabetes. A higher degree of randomness leads to a lower autocorrelation. In spite of this, at time scales greater than 10 s, the observed differences in the parameter were not statistically significant.

A comparison of the average perfusion in DM and control groups of different ages using the LDF method is shown in Fig.5a. According to the presented data, blood microcirculation index values increase with age and with DM development. There were no statistically significant differences between patients and older controls in average perfusion. The results are consistent with previous studies that reported higher LDF signals in patients with DM compared with healthy controls [23], [39], [40].

There is ambiguity regarding skin blood flow in DM under basal conditions. According to some researchers, [41] patients' blood flow is reduced, while others [23], [39], [40] claim higher values. Most studies report no significant differences in average perfusion at rest. There may be differences in results due to different study methodologies, different areas of measurement, and a general heterogeneity in skin perfusion. According to some studies, patients with diabetes have greater average perfusion due to neuropathy development, which results in a reduction in arteriole vasoconstriction and an increase in blood flow in arteriolo-venular anastomoses [40], [42].

As shown in previous studies by the authors of this paper [43], [44], patients with DM, which is characterised by a longer duration of disease and aggravated complications, had a higher LDF signal at basal than the control group. Meanwhile, patients without significant concomitant complications or at an earlier stage of the disease had lower perfusion values than controls. There were no statistically significant differences between the three groups.

The mean energy of blood flow oscillations, as shown in Fig. 5b, was reduced in patients with DM in the endothelial, neurogenic, myogenic, and respiratory ranges. In terms of neurogenic and myogenic fluctuations, statistically significant differences were found between the group of patients with DM and older controls, reflecting the influence of sympathetic nervous innervation and vascular smooth muscle activity.

Diabetes-related microcirculation disorders are most commonly characterised by disturbances in the functioning of smooth muscles, endothelial cells, and perivascular nerves at the periphery, which explained the reduced values of low-frequency perfusion fluctuations we observed. A study of animal models of diabetes also showed that disturbances in peripheral vessels' nervous innervation are the first factor contributing to microcirculatory dysfunction, which leads to endothelial dysfunction and impairments of smooth muscle function within the vascular system [45].

In another study, diabetic patients had significantly lower values of low-frequency endothelial, neurogenic, and myogenic oscillations as compared with healthy controls [46] when measuring levels near the first metatarsal head. Because the LDF signal recording in our study was shorter, fewer fluctuations in this range could be recorded, which may explain the lack of significant decrease in endothelial fluctuations. When measuring glabrous skin, Jan et al. [23] also showed decreased neurogenic and myogenic regulation in diabetes in response to heat. According to the authors, such changes in blood flow regulation are attributed to disruptions in the autonomic component of the peripheral nervous system, causing blood flow to be redirected to the shunts.

In addition to a general decrease in the energy of low-frequency oscillations, our results indicate a tendency towards an increase in the values of fluctuations in the cardiac range in patients (a statistically significant increase relative to the control group of young people). This frequency range reflects

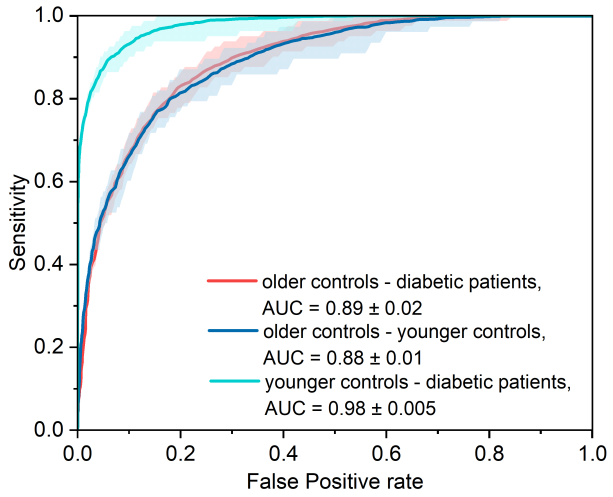

Fig. 7. Average ROC curves for the delineation of classes "young controls - diabetic patients", "older controls - diabetic patients", "young controls - older controls" using logistic regression and energy of blood perfusion oscillations and average blood perfusion measured in wrists. Scattering shows ranges of maximal and minimal deviation from average curve.

the degree of elasticity of the vascular wall and the amount of blood flowing through the arterial side of the microvasculature [47]. According to the [48] study, our results suggest that patients with DM are more likely to have stiff vascular walls due to a buildup of advanced glycation end products. In response to a decrease in the activity of other regulatory factors, arterial inflow into the microvasculature may increase as a compensatory mechanism.

B. Logistic regression based predictive modelling

As a result of identifying statistically significant differences between groups of volunteers for several parameters estimated from blood perfusion time-series, we used those parameters as a feature set for detecting corresponding health conditions. The problem of feature selection for classification is a trade-off between model complexity and performance, so it is important to evaluate the performance of the model on a validation set after the feature selection process. The procedure included tests of the logistic regression model with the evaluation of classification performance of different feature subsets. The feature subset that resulted in the best performance was selected for the model.

The best performance was achieved for the delineation of the groups of older and young volunteers by using parameters for cardio, myogenic, and neurogenic perfusion oscillations. In terms of accuracy and AUC, 0.82 ± 0.02 and 0.88 ± 0.01 were obtained. With the same feature set, the highest performance was achieved for the delineation of older volunteers and diabetic patients. Based on the metrics obtained, the accuracy was 0.80 ± 0.02, and the AUC was 0.89 ± 0.02. The feature set composed of parameters of energy for cardio and myogenic perfusion oscillations was most effective in delineating young volunteers and diabetic patients. Based on these metrics, we obtained accuracy of 0.92 ± 0.1 and AUC of 0.98 ± 0.005. Input feature vectors with a higher dimension did not improve classification accuracy. Fig. 7 demonstrates average ROC curves obtained for the delineation of classes "young controls - diabetic patients", "older controls - diabetic patients", "young controls - older controls" using logistic regression and energy of blood perfusion oscillations and average blood perfusion measured in wrists.

IV. Conclusion

In this study, wireless portable dynamic light scattering sensors combined with laser Doppler flowmetry signal processing were presented and tested to detect microvascular changes associated with diabetes and ageing in wrist skin. Overall, the ability of wireless portable sensors to continuously monitor blood perfusion in real-time has the potential to revolutionise the way we diagnose and treat health conditions that are characterised by system changes in skin microvasculature. The conducted tests confirmed that the blood flow measurements by the novel devices possess comparable sensitivity with conventional table-top laser Doppler flowmetry systems when the hand on which the measurements are taken remains motionless. Due to motion artefacts, the sensing system can only partially be classified as wearable, since walking measurements are limited. Nevertheless, the development and research carried out pave the way for a completely wearable system to be developed in future. The blood flow sensors can be used to monitor blood perfusion at rest and provide important insights into the progression of diabetes and its complications. Potentially, this can help physicians to make more accurate and timely diagnoses and to develop more effective treatment plans for patients with diabetes.

V. Ethics Statement

The study was carried out in accordance with the Declaration of Helsinki principles and approved by the Ethics Committee of the Orel State University (meeting protocol no. 15 of February 21, 2019). All healthy volunteers and patients who participated in the trials gave their full consent to these measurements in writing and were informed of their right to discontinue participation at any time.

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