Optical Non-invasive Flowmetry without Lasers and Coherent Light

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Keywords: Laser, Flowmetry, Blood Flow, Doppler Effect, Tissue, Spectrum, Intensity, Fluctuation, Incoherent Light.

Abstract: Laser Doppler Flowmetry (LDF) and other optical technique to measure a blood flow in tissues noninvasively (*in vivo*) are well-known today. Meanwhile, in spite of more than 40-year history, they do not have applications in real clinical practice yet. This situation could be a consequence of incorrect understanding of the physical basics of these methods and, accordingly, of insufficient hardware design, software algorithms, as well as of erroneous interpretation of the data measured. The basic theory of physical principles of LDF is the model developed by R.Bonner and R.Nossal in 1980. However, it does not describe many phenomena, low-frequency fluctuations of optical fields due to a variable blood content in a tissue diagnostic volume, for example. In this study, we assumed that the low-frequency part of the power spectrum could provide the same information about the blood flow as the middle- and high-frequency parts provide it in LDF. Moreover, we proposed the use of coherent light source could be avoided in this case. We have developed a much simpler and low-cost LED-based prototype and confirmed our assumptions in experiments. Thus, we proposed a new technique to build simple and economic optical diagnostic tool to evaluate a blood flow in tissues.

1 INTRODUCTION

Optical noninvasive diagnostic techniques, which use lasers and coherent light for assessment of a tissue blood flow, such as Laser Doppler Flowmetry (LDF), Laser Speckle Contrast Imaging (LSCI), etc., are well-known today. All of them have already proven its usefulness in a number of medical disciplines (Briers, 2001), (Rajan et al., 2009), (Roustit et al., 2012). However, in spite of more than 40-year history, they are not used yet in a clinical practice daily. They have many implementations in different medical research, but their practical applications, without which a practicing clinician cannot work today, are not known. Large fluctuations of the output as well as a low reproducibility of the result often lead to an inability of the personal diagnostic conclusion with the use of this technique. Only at scientific studies in groups of patients, when data are averaged in groups, there are steadily observed significant differences in groups.

In our opinion, this situation can be a consequence of incorrect understanding of the physical basics of these methods and, accordingly, of not enough correct hardware design, software algorithms, as well as of erroneous interpretation of the data measured. If to consider, for example, the LDF technique, anyone can see that in the LDF theory the formation of low-frequency components of the input optical signal is poorly explained. The basic theory of forming the optical input signal in LDF is the well-known model developed by R. Bonner and R. Nossal (B&N model) (Bonner and Nossal, 1981). Physically based on the light-beating spectroscopy (Cummins et al., 1970) and the Doppler effect at light scattering on moving red blood cells (RBCs) (Nilsson et al., 1980), this model became the most used and, practically, the almost single-used theory of LDF. Authors derived and introduced a power spectrum of the analyzed signal in the form of the exponential decay, similar to a fractal noise ($1/\omega$ noise, where ω is a frequency). This power spectrum was then well confirmed in

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Rogatkin, D., Lapitan, D. and Persheyev, S.
Optical Non-invasive Flowmetry without Lasers and Coherent Light.
DOI: 10.5220/0009098402150220
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 1: BIODEVICES*, pages 215-220
ISBN: 978-989-758-398-8; ISSN: 2184-4305

experiments (Obeid et al., 1988). However, the nature of the spectrum can be different, controversial and debatable, in our opinion. In the B&N model, this spectrum on a photodetector's surface is only formed by the coherent light beating components due to a heterodyne mixing of the initial probing optical field and the field having a Doppler frequency shift at light interaction with moving RBCs inside vessels. Neither the unsteadiness of scattering properties of tissues surrounding the vessels due to their compression by pulsating vessels' walls, nor any low-frequency fluctuations (LFFs) of RBCs amount in a diagnostic volume are not taken into account. Meanwhile, in recent years a number of authors showed that LFF in tissue scattering properties can be reflected in the registered optical signal (Nippolainen et al., 2015), that variable RBCs content in a diagnostic volume may play an important role in formation of a low-frequency part of the power spectrum (Lapitan and Rogatkin, 2016), or that in LDF the same power spectrum *P(ω)* can theoretically be derived from completely other assumptions (Lapitan et al., 2017).

Therefore, in this study we proposed that the low-frequency part of the power spectrum could provide the same information about the blood flow as the middle- and high-frequency parts of it. Moreover, we proposed that the coherent light is not mandatory to form and to detect these LFF. We have developed a novel, simple, not expensive LED-based prototype and confirmed our assumptions in experiments.

2 THEORETICAL BACKGROUND

Due to the LDF and LSCI methods are the most prevalent at present, as well as due to their results can be converted into each other so that they can be considered as of the one family techniques (Bi et al., 2015), (Fredriksson et al., 2016), we will only consider in this study the LDF theory, the B&N model, in particular. The main theoretical statement of the B&N model, which is also used in all other versions of the LDF theory (Fredriksson et al., 2007), (Binzoni and Martelli, 2017), is that the blood *Perfusion Index* (PI) or the *Blood Flow* (BF) can be determined by analysis of the spectral power density of the recorded photocurrent (Bonner and Nossal, 1981), (Nilsson et al., 1980). A number of authors use the amplitude spectrum of the photocurrent or a photovoltage (Obeid et al., 1988), (Rajan et al., 2009), but this does not greatly affect the output.

In the case of a photocurrent power spectrum, BF in LDF is determined by the equation:

$$BF_{LDF} = \frac{k_0}{\langle i(t)\rangle^2}\int_{\omega_1}^{\omega_2}\omega \cdot P(\omega)d\omega\,. \qquad (1)$$

Here ω denotes the angular frequency, $P(\omega)$ – the power spectrum or the amplitude spectrum of a photocurrent $i(t)$, k_0 – a dimensional coefficient of a proportionality. In the case of a power spectrum, $P(\omega)$ can be calculated with the use of the well-known Wiener–Khintchine theorem (Cummins et al., 1970):

$$P(\omega) = \int_{-\infty}^{+\infty}\langle i(t)i(t+\tau)\rangle e^{-j\omega\tau}d\tau\,. \qquad (2)$$

The typical in LDF power spectrum $P(\omega)$ *of* a photocurrent $i(t)$ is presented in Figure 1.

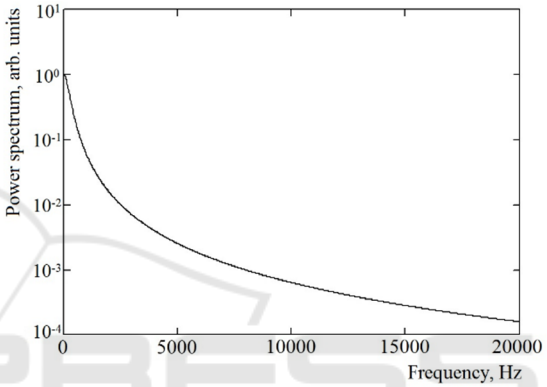

Figure 1: The typical power spectrum $P(\omega)$ of a photocurrent $i(t)$ described in the B&N model by Eq.2.

In the case of a photocurrent amplitude spectrum, an equation similar to Eq.1 is used to calculate BF. The only difference is in the constant k_0 and in the normalization parameter $\langle i(t)\rangle^2$. Normalization for photocurrent amplitude spectra should be performed using the constant component of the photocurrent $i_{dc}=\langle i(t)\rangle$. Thus, to evaluate BF in tissues the power spectrum or the signal amplitude spectrum is only the key input physical values for data processing. Factors that form these spectra do not play any important role for the explored problem.

Usually, in LDF the region of the Doppler effect ranges from ω_1=30 Hz to ω_2=30 kHz (Koelink et al., 1994). Below 30 Hz a photoplethysmographic effect and motional artifacts are considered dominant. Therefore, the lower waveband is assumed to be not useful to calculate BF (Bonner and Nossal, 1981) and, so, reputedly, not used in LDF-meters by means of hardware filtering.

Nevertheless, in many publications the spectral density of a photocurrent or a photovoltage amplitude spectrum covering the range 1-500 Hz with a maximum of amplitudes at units or tens of Hz are

presented (Obeid et al., 1988), (Hu et al., 2013). For example, Figure 2 represents the *i(t)* spectrum measured in a portable LDF-meter (Hu et al., 2013).

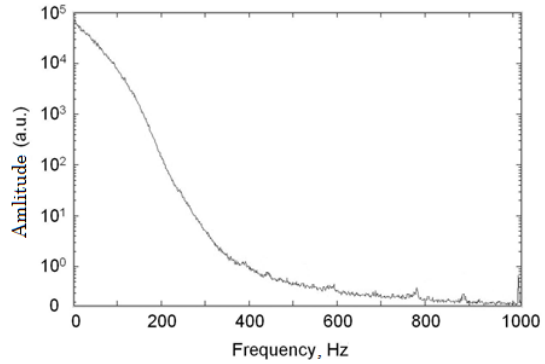

Figure 2: The low-frequency spectrum of the *i(t)* inside a portable LDF-meter (Hu et al., 2013).

Recently it was additionally showed (Lapitan et al., 2018), that in a number of commercially available LDF-meters, LFFs of the input optical signal can pass to the output and can influence on the BF calculated through the normalization parameter (denominator) $<i(t)>^2$. Usually, this mean value is calculated with the use of a time window of approximately 0,5-1 second. Therefore $<i(t)>$ can have LFFs below 1-2 Hz. Being squared this will give a wider range of the spectrum. Generally speaking, LSCI technique is based on the temporal LFFs of the speckle pattern contrast or of the field correlation function $g^{(1)}$ at a coherent illumination, as well (Fredriksson et al., 2016). In LDF, the existence of the optical LFFs in a tissue microvasculature at external illumination by stationary-power laser light is now well confirmed both in experiments (Mizeva et al., 2015), (Mizeva et al., 2016), and theoretically (Lapitan and Rogatkin, 2016). In the latter case, LFFs were derived as a result of a variable blood content in the microvasculature. However, the B&N model does not describe any LFFs of optical signals. The model was formulated at the assumption, that amplitudes of all scattered fields are stationary. In the theory, the blood volume in a microvasculature is stationary, as well. However, inside alive tissues these assumptions are wrong.

In our theoretical assumption, we relied on a number of recently published data mentioned above. First, we took into account that variable hyperaemia can form LFFs of the input optical signal (Lapitan and Rogatkin, 2016). Then, we considered the opinion and experimental data that vessels' walls motions at hart beating compress surrounding connective tissues changing their optical properties (Nippolainen et al., 2015). At last, we took into consideration the fact that the denominator $<i(t)>$ can have LFFs, as well. All these phenomena form the total LFFs spectra of the registered and processed signal, which can be used to calculate BF similar to LDF technique, but with the use of the low-frequency waveband, below 30 Hz. Moreover, we assumed, in this case coherent light to form LFFs and to evaluate BF is not mandatory, so light emitted diodes (LEDs) can be used as a source of optical radiation. This technique we named as *Incoherent Optical Fluctuation Flowmetry* (IOFF).

3 EXPERIMENTAL PART

3.1 Experimental Prototype

An experimental LED-based prototype that performs the above method for measuring the skin BF (the skin blood perfusion) was developed. The appearance of the prototype is shown in Figure 3.

Figure 3: The appearance of the developed prototype for measuring the skin blood flow (BF).

The prototype consists of the external optical probe, the main electronic unit and a laptop with the special software. In the optical probe, six green-light LEDs for illuminating the examined skin are placed radially around a photodetector - a silicon photodiode – to provide a uniform illumination. The photodiode registers backscattered radiation from a diagnostic volume of skin under the optical probe. The narrow-band radiation in the green spectral range of 560–580 nm was selected as probing radiation to use the corresponding isosbestic point, at which the light absorption by oxyhemoglobin and deoxyhemoglobin in blood is equal. It prevented inaccuracies associated with different light absorption by venous and arterial fractions of blood in the diagnostic volume, because

the total signal from skin was collected by the photodiode regardless of the percentage of oxyhemoglobin/deoxyhemoglobin concentrations in the tested volume of skin (diagnostic volume).

Incoherent illumination, LEDs, and the waveband below 30 Hz allowed us to perform a pulsed regime of the skin illumination. It is useful to avoid complex differential scheme of the signal registration, which is often used in LDF to compensate ambient light and which is a source of the false spectra formation inside the instrument (Lapitan et al, 2018). We used the pulsed switching-on/switching-off regime for LEDs with 50% duty cycle. The 320 Hz operating frequency was chosen to satisfy the Nyquist criterion with the 5-fold margin. During the switching-on time of LEDs total backscattered probing radiation together with existing ambient light were registered, while during the switching-off time of LEDs the backscattered ambient light was only registered and analysed. Subtracting the ambient light signal from the total signal registered, we eliminated the ambient radiation impact on the registered probing radiation.

The purified from ambient light signal was further amplified, digitized at the frequency of 320 Hz, and processed in a laptop by the LabVieW-based software to compute BF (Figure 4).

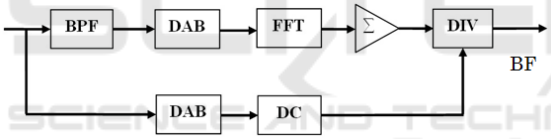

Figure 4: The block-diagram of data processing. BPF is the band-pass filter, DAB is the data accumulation buffer, FFT is the Fast Fourier Transform module, Σ is the adder, DIV is the divider, DC is the unit for extraction of the <*i(t)*>.

We used the photocurrent *i(t)* amplitude spectrum technique to compute BF. First, the *ac* component of the signal is extracted by a band-pass numerical Butterworth filter (BPF) of the 2nd order (see the upper way of the block-diagram). The frequency range was chosen as follows: ω_1=0,5 Hz and ω_2=12 Hz. Next, the *ac* signal is accumulated in the data buffer (DAB) within each 1 second. For this purpose, a buffer sample size of 320 points was used. These 320 points are then directed every second to the Fast Fourier Transform (FFT) module, where the amplitude spectrum of the signal is formed. The resolution of such a spectrum is 1 Hz. Finally, all spectral components are summed in the adder Σ with corresponding frequency weights (numerical integration) and divided by the *dc* component of *i(t)*. The *dc* component is obtained by averaging of all 320 signal magnitudes on the time interval 1 second (see the lower way of the block-diagram). Thus, BF points are formed as the output every 1 second.

To perform functional tests with skin heating, a heating metal plate was incorporated in the optical probe. Heating was performed by a pulsed current with a pulse-width automatic modulation. An operator can set the desired heating temperature of the plate with a given heating rate.

3.2 Experimental Study and Results

At the initial step of our experimental study, to confirm the presence in the spectra the proposed LFFs at a continuous incoherent illumination of the tested skin, we measured a photocurrent power spectrum after the photodiode with the use of the standard spectral equipment (L-CARD spectral analyzer, RF). Figure 5 represents the typical spectral power density of *i(t)* at the green-light LEDs illumination of the fingerprint skin area of a volunteer.

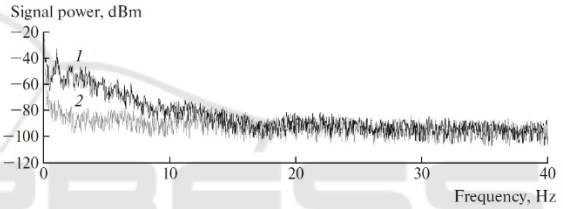

Figure 5: Typical spectral power density of *i(t)* in *in vivo* experiments. 1 - Healthy volunteer at a rest. 2 - Healthy volunteer at the shoulder arterial occlusion.

As one can see, the normal blood flow in arms forms visible LFFs in the spectral range 0-12 Hz, while the arterial occlusion blocks LFFs. It confirms well our assumptions. Doppler components in *i(t)* are not presented in these spectra due to the absence of the coherent illumination. It is also interesting to note that the blood-pulsed spectral components with the frequency of around 1 Hz are a visible part of the total LFFs spectrum (see the spectrum 1), but they do not form the power spectrum completely, as it might seem from the theory of a photoplethysmography.

In addition, at the arterial occlusion we measured and analyzed a behavior of the photovoltage *dc* component. Like for a photocurrent, the photovoltage *dc* component was calculated by averaging all 320 digitized signal points on a time interval of each one second. Figure 6 shows the example of the behavior and a corresponding BF computed with the use of this photovoltage *U*. The example clearly shows a decrease in *ac* components of the signal (decrease in LFFs), and an increment Δdc of the *dc* component of *U* at arterial occlusions.

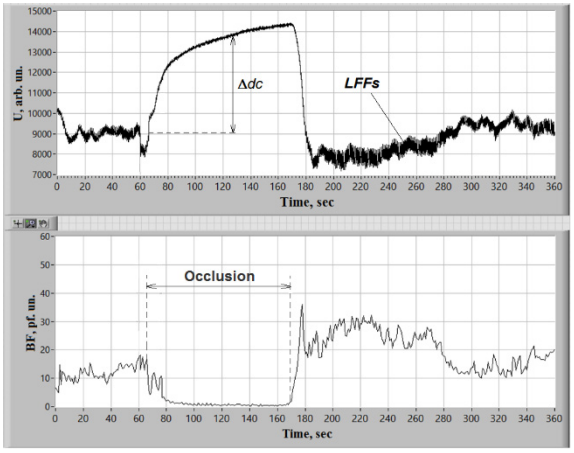

Figure 6: Example of the recorded *dc* photovoltage *U* during a test with the shoulder arterial occlusion and the corresponding BF computed.

Final steps of this our experimental study were comparative measurements of BF with the use of our new method and a standard LDF technique. Standard LDF-meter LAKK-02 (LAZMA Ltd., RF) working at the isosbestic point 808 nm was used as the reference tool. Functional tests with skin heating and arterial occlusion were carried out for the comparative study. Figure 7 shows the design of the study. BF was simultaneously measured in the outer side of a forearm by IOFF optical probe (1) and by the standard LDF optical fiber probe (2). To execute a test with skin heating under the fiber optical probe, an external heating probe was used. Final heating temperature for both probes was 42^0C. The same arm was explored to execute tests with occlusion. Occlusion pressure was applied by a standard tonometer's cuff inflation.

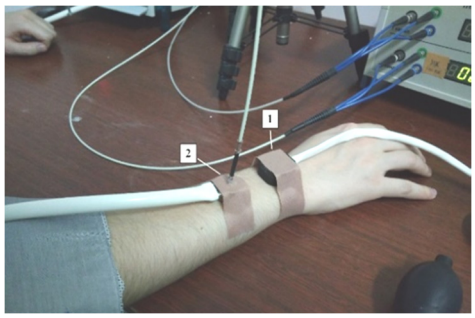

Figure 7: Design of the comparative study.

To made results of two different measurements comparable in BF magnitudes (in *pf. un.* - perfusion units), it was necessary to select properly the proportionality coefficient k_0 for the IOFF technique in the main Equation 1, because for the standard LDF-meter it was already embedded in its software and not changeable. The needed value of the coefficient k_0 for new IOFF technique was obtained by means of the selection of the approximate equality of BF magnitudes during the first test with occlusion.

Examples of the recorded BFs in these final experiments are shown in Figure. 8.

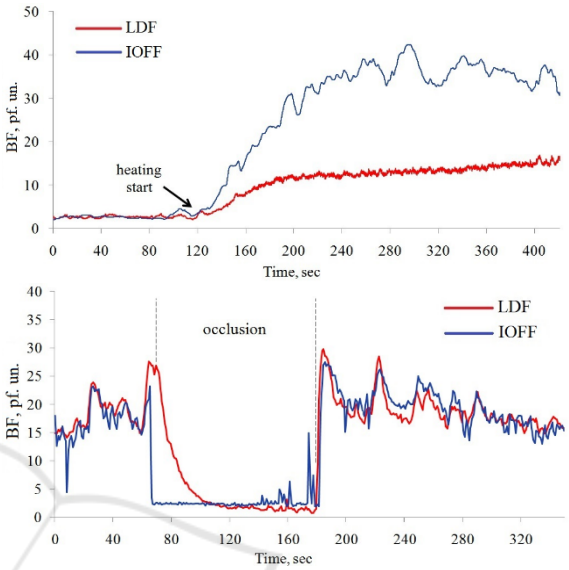

Figure 8: Examples of the recorded BF during heating (top) and arterial occlusion (bottom) tests with the simultaneous usage of IOFF and LDF techniques.

As seen in the Figure 8, the measured BFs were similar even in details at arterial occlusions, while at the heating test IOFF technique showed the enhanced sensitivity. Probably, it is a consequence of different wavebands used – green in the IOFF case and near infrared in the LDF one. Nevertheless, the result is visible. Our assumptions were confirmed well.

4 CONCLUSIONS

Relying on a number of recently published data, in this study we assumed a strong influence of low-frequency fluctuations (LFFs) in registered optical signals on the final output in LDF. LFFs form the low-frequency spectra of all processed signals, and can be used to calculate BF similar to LDF technique, but using the waveband below 30 Hz. Moreover, we assumed that the coherent illumination and lasers to evaluate BF is not mandatory in this case. This technique we named as IOFF - *Incoherent Optical Fluctuation Flowmetry*. We developed a LED-based prototype that performs IOFF, and carried out a number of experiments to confirm our assumptions.

Most of our experiments confirmed assumptions we made well. LFFs were registered with incoherent illumination in skin. The main spectral range of LFFs was determined between 0 and 12 Hz. It allowed us to calculate BF similar to the LDF algorithm, but inside the waveband below 30 Hz. Comparative measurements of BF using our novel method and a standard LDF technique showed a good similarity of the results. Measured BFs were equal even in details at arterial occlusions, while at heating tests IOFF technique showed the enhanced sensitivity. These positive results open a way for building novel and less sophisticated than LDF optical diagnostic tools for assessment of BF in tissues. Of course, the proposed IOFF technique needs further detailed investigations, especially in clinics to prove its clinical significance. However, as one can see, our approach already has a number of additional advantages. One important advantage is the cost of the equipment. A commercial LDF-meter such as the Moor VMS-LDF costs more than 10,000 USD. The cost of our self-designed portable prototype is less than 100 USD (including all components except a computer). The second one is not sophisticated and clear metrology. The metrology in LDF is sophisticated due to a complexity with the design of tissue-like phantoms imitating the motion of RBCs in a microvasculature bed. In our case, an imitation of the amplitude modulation of the probing radiation with different modulation depths on the background of different levels of the *dc* component of the backscattered radiation is sufficient.

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