Multifunctional Laser Noninvasive Spectroscopic System for Medical Diagnostics and Metrological Provisions for That

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ABSTRACT

This paper describes a new multifunctional laser noninvasive diagnostic system (MLNDS) for medicine. In a single hardware MLNDS combines 3 different *in vivo* laser diagnostic techniques: Laser Doppler Flowmetry, Laser Fluorescent Diagnostics and Reflectance Tissue Oximetry. All these methods together allow a doctor to evaluate more exactly and *in vivo* a functional condition of soft tissues, especially to study the finenesses of respiratory and blood microcirculation processes in a skin and mucosa. The complex complementary diagnostics turns out to be more powerful than a trivial sum of isolated one. To produce more precise measurements a number of problems of metrological providing for that have been studied as well as a set of simple, reproducible and photostable calibration gauges with tissue-like optical properties has been created.

Keywords: Medicine, noninvasive, *in vivo*, spectrophotometry, laser, tissue, diagnostics, metrology, accuracy, gauges

1. INTRODUCTION

In recent 10-15 years a general medical practice has been successfully enriched with different new methods of noninvasive optical diagnostics such as a Laser-Doppler Flowmetry (**LDF**), Laser Fluorescent Diagnostics (**LFD**), Tissues Reflectance Oximetry (**TRO**), etc., which all in totality we call a *Medical Noninvasive Spectrophotometry* (**MNS**)[1]. All these methods allow a doctor to evaluate *in vivo* and more exactly a clinical functional condition of soft tissues, especially to study the finenesses of respiratory and blood microcirculation processes in a skin and mucosa[1,2]. In this our paper we'd like to describe a new our multifunctional laser noninvasive diagnostic system (**MLNDS**) for medicine which combines LDF, LFD and TRO diagnostic techniques in a single, united equipment, what makes it possible to use them together, simultaneously during one diagnostic procedure to collect all necessary MNS-diagnostic data from the same anatomic "point" of the examined tissue. This way of development of a modern MNS and some advantages of that in a modern medicine were predicted by us previously[1]. Basic principles of hardware's and software's architecture for such complex diagnostic systems were studied and described recently as well[3,4]. Today a number of scientific groups all over the World go this way combining different MNS diagnostic technique in their fundamental research[5]. Our first compact pilot prototype of MLNDS (made by *SPE "LAZMA" Ltd., RF*) goes now a real clinical trial at Moscow Regional Research and Clinical Institute "MONIKI" named after M.F.Vladimirskiy. One of the studied questions today in our research is an accuracy and reproducibility of all medical diagnostic data which are obtained with the help of MLNDS as well as a necessary metrological support for that to produce more precise measurements.

2. DIAGNOSTIC SYSTEM AND ALL REGISTERED MEDICAL PARAMETERS

The pilot prototype of MLNDS (see Fig.1) is a small opto-electronic and low-energy laser diagnostic system with an operating computer. The used spectral waveband in it is 360-1000 nm. It is table-held diagnostic equipment having an

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optical fiber cord in a capacity of diagnostic probe. So it is useful both for different external clinic examinations and for various inner endoscopic (gastroscopic, etc.) procedures.
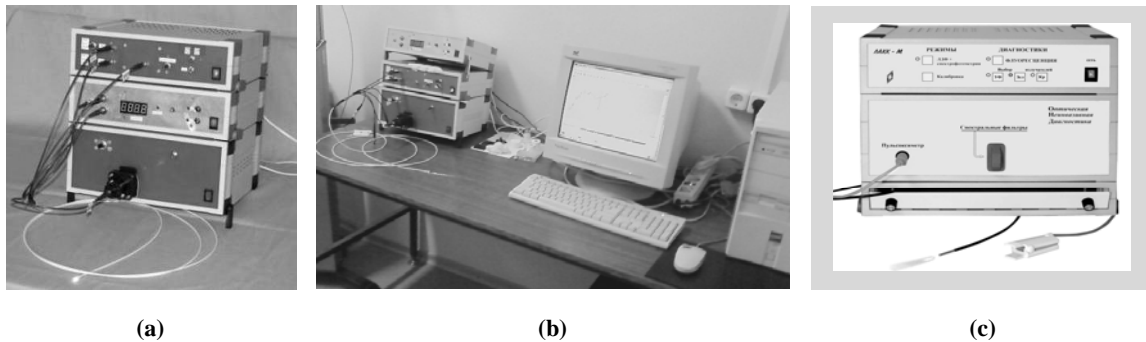

(a)   **(b)**   **(c)**

Fig.1. First compact pilot prototype of MLNDS.
(**a**) – an experimental design; (**b**) – an example of a table location with computer in doctor's cabinet;
(**c**) – a proposed design of the serial product with additional pulsoximetry probe.

MLNDS consists of a number of typical and some special lasers, optical and electronic units (lasers drivers, spectrometer, photodetectors), etc. which are integrated in a united complex diagnostic hardware (Fig.2). In source unit 1 under the control of laser drivers 2 a number of laser modules 3.1…3.n produces necessary laser light energy, which flows through optical connectors 4.1…4.n into different optical fibers of optical cord 5 and then into a tested tissue 6. In tissue the laser light being absorbed and scattered by inner chromophores and heterogeneities induces some fluorescent as well as backscattered secondary radiation, which particularly flows back to the tissue's surface. On the surface the induced secondary radiation is collected by the same multifiber optical probe 5 and then transferred back to the MLNDS to an analyzer unit 7. In the unit 7 one part of the collected secondary radiation through an optical collimator 9 passes into spectrometer 8 to analyze a spectral composition of the fluorescent flux. Another part of that goes through optical connectors 12.1…12.3 and optical filters 11.1…11.3 into special units 13 and 14 in which a power of collected radiation of each used initial laser wavelength (unit 13) as well as a Doppler shift of initial frequency of laser radiation (unit 14) are analyzed. A computer 15 operates MLNDS in a total.
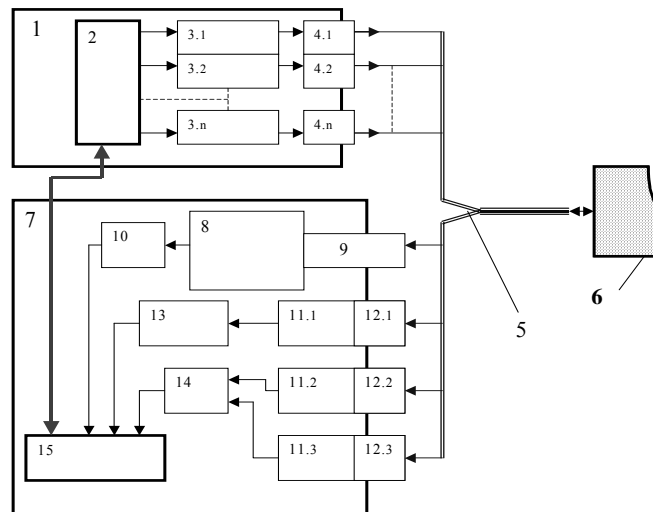

Fig.2. Schematic hardware setup of MLNDS.

All diagnostic data are collected and processed in MLNDS with the use of special complex and multilevel software[4]. At first level of data processing all digital physical data from all photodetectors containing main initial diagnostic information are translated into the form of main physical functional dependences (amplitude versus time, amplitude

versus wavelength, etc.) and then are presented to user in a graphic mode on a screen of computer's monitor. At next, second level of data processing the key inverse problem of light distribution and scattering in tissue are resolved. All these inverse calculations in MLNDS are based on a modified analytical Kubelka-Munk approach[6,7]. As a result of that the modified transport optical properties of tested tissue are stored in a memory of computer what allows at next steps of calculation to yield all important medical parameters describing a biochemical composition of the tissue. Final (third) level of software algorithms allows a doctor to form a database of patients and to calculate for them all final medical diagnostic parameters which are summarized both from basic diagnostic data of each diagnostic technique and from additional united data what are obtained from additional cross-calculations. First of all we mean a number of parameters which characterize some respiratory and blood microcirculation processes in tissues, namely:

- tissue's blood perfusion (**M**) as a function of time (**FOT**);
- functional transcutaneous saturation of oxy-hemoglobin fraction in a mixed peripheral blood (S_tO_2) as a FOT;
- relative volume of all fractions of hemoglobin (total hemoglobin) in a tested tissue's volume (V_b) as a FOT;
- an index of a perfusional saturation of the oxygen in a blood ($S_tO_2m=S_tO_2/M$) as a FOT[8];
- a parameter of a specific oxygen utilization (uptake) in a tissue (**U**) as a FOT.

It must be special noted, that parameter S_tO_2 unlike conventional pulsoximetry is registered and calculated in MLNDS as an average value between venous ($S_tO_2^v$) and arterial ($S_tO_2^a$) saturation, close to venous saturation. So, the evaluation of specific oxygen uptake U in a tissue becomes possible[8]:

$$U = (S_tO_2^{\ a} - S_tO_2)/V_b \ . \tag{1}$$

Additionally, a number of data processing algorithms have been included in the system's software to calculate all typical frequencies and magnitudes of existed biological rhythms of microhaemodynamics in the tested tissue's volume (miogenic rhythm, neurogenic one, etc.). In accordance with conventional data interpretation in LDF these rhythms characterize a functional state of the microcirculatory regulation what is important for various applications in a modern and evidence based medicine[2].

Moreover, all mentioned above final medical parameters (M, S_tO_2, V_b, etc.) with the use of MLNDS can be measured together as a function of time during any conventional functional tests and procedures with experimental loads on the system of microcirculation. For example: test with occlusion (see Fig. 3), test with a heating (cooling), medicinal test, etc. Most of these tests can't be applied to a patient several times during one diagnostic procedures what makes it not possible to use different diagnostic technique (LDF, TRO, etc.) one after the other. So, the complex complementary diagnostics with the use of MLNDS turns out to be more powerful tool than a trivial sum of isolated one.
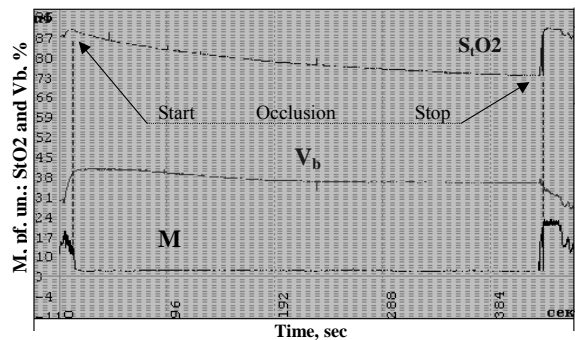

Fig. 3. An example of combined LDF and TRO diagnostic data versus time in the case of a functional test with arterial occlusion. All data collected from a finger tip. Local occlusion was applied to third phalanx of the finger. Time of occlusion - 6 min.

To calculate a numeric diagnostic criterion in a case of autofluorescent data processing in LFD technique we have used in the system's software our standard methodology[9-12]. In accordance with that the modified fluorescent contrast coefficient K_f in different waveband for different excitation wavelength is calculated, what indicates an existed biochemical composition in tissues on a level of cells' fluorescing respiratory enzymes: flavins (**FP**), **NADH**, lipo-pigments (**LP**), protoporphyrins (**PP**), etc. For different waveband and different excitation wavelength K_f characterizes a presence or absence of the endogenous enzymes in a tested tissue's volume. As it is well-known, the relative

concentrations of them are a quite good indicator of various metabolic processes in tissues and organs. It allows a doctor, in instance, to estimate a chronic hypoxia area in tissues what is very important, for example, in the modern radiology[9], gastroenterology[10] and angiology[11].

A typical registered fluorescent spectrum of oral mucosa in a case of 532 nm excitation wavelength is shown in Fig.4.
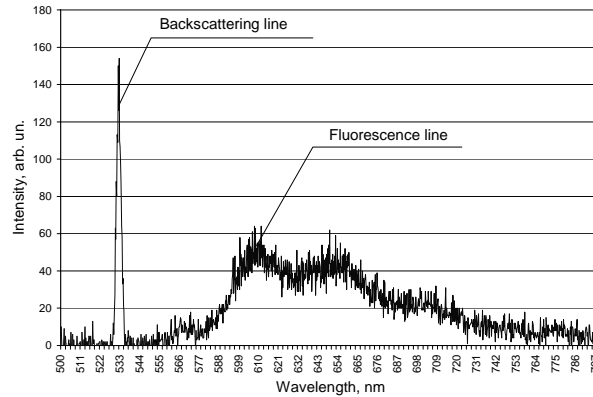

Fig. 4. A typical autofluorescent spectrum of oral mucosa (excitation line is 532 nm).

All coefficients K_f are calculated in MLNDS with the use of general formula[12]:

$$K_f = 1 + (I_f \cdot \beta - I_{bs})/(I_f \cdot \beta + I_{bs}) , \qquad (2)$$

where: K_f is the modified fluorescence contrast coefficient ($0 < K_f < 2$); I_f – registered light flux intensity in the maximum of a fluorescence spectrum's lines; I_{bs} - intensity of the registered backscattered laser radiation in the excitation line; β - device's reduction coefficient ($\beta \approx 1000$ to reduce I_{bs} to comparable level with I_f).

The switching between different spectral channels (between different β) in a pilot model of MLNDS is made in manual mode by means of replacing of different optical filters. Together with data on microhaemodynamics various contrast coefficients K_f help a doctor to form a total diagnostic conclusion about functional state of the tested tissue. For example, in oncology, it is well known that different processes of blood microcirculation and tissues oxygenation in malignant tumors have a strong influence on a radiotherapy efficacy. But there are in the modern radiology only few methods to prognosticate a positive radiotherapy outcome. So, today, for this purpose the united possibilities of LDF, LFD and TRO diagnostic technique are irreplaceable at all[9,14].

Thus, MNLDS allows a doctor to execute a dynamic and multi-parametrical diagnostic examination of patient's soft tissues on the microcirculatory and biochemical levels *in vivo*. It is very effective in different brunches of medicine: in oncology[9], gastroenterology[10], occupational diseases therapy[11], etc. So, we can say with a confidence that in the up-to-date MNS the mentioned above set of medical diagnostic parameters is a unique set in a real medical practice today.

3. ACCURACY AND METROLOGICAL PROVIDING OF DIAGNOSTICS

It has been shown 10 years ago[12] that for a laser fluorescent diagnostics (LFD) a total random error of *in vivo* measurements could reach a quite high level – around 40%. The same order of errors and a random standard deviation of the final medical diagnostic data had been reported recently for TRO diagnostic technique[13]. So, one of the important questions today is an accuracy and reproducibility of all complex medical diagnostic data produced in MNS as well as a necessary metrological support for that to produce more precise measurements. Up to now all these metrological problems were touched upon a question in a literature only a little bit yet. One of the first papers on this problem was the mentioned above paper by D.Rogatkin et. al.[12]. Today we are trying to study some metrological problems in MNS more widely and detailed.

For this purpose a novel design of a set of solid calibration gauges (measures) with tissue-like optical properties was made (Fig. 5). The gauges are photostable and easily reproducible. They consist of a light scattering foundation and a number of spectral absorbing, scattering and fluorescent thin polymer films-layers (Fig.6). If fluorescent layers are presented, then LFD channels of MLNDS may be tested and calibrated. In other case another diagnostic technique (TRO, for instance) can be tested without any fluorescent signals. Simultaneous measurements are possible as well.
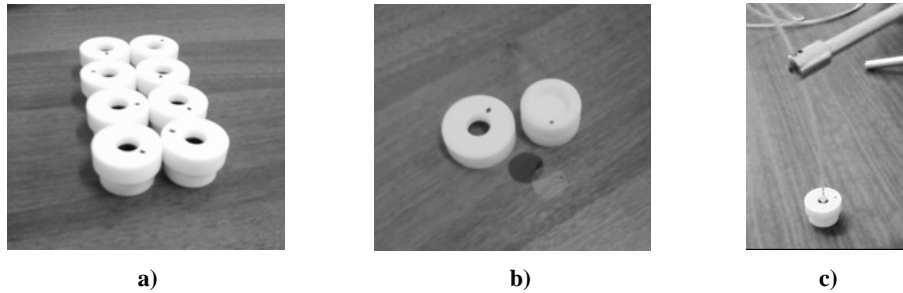

a)   **b)**   **c)**

Fig. 5. A set of calibration gauges (**a**). Constructive specialties of the gauge (**b**).
An example of a calibration procedure (**c**): an optical fiber probe of MLNDS is fixed in a stand.
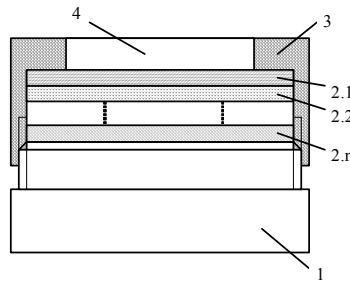

Fig. 6. Some constructive specialties of the calibration gauges.
1- a scattering foundation, 2.1…2.n – different absorbing, scattering and fluorescing standard thin polymer films,
3 – a frontal lid with a window 4 for an optical probe;

Different sets of gauges were created for different diagnostic techniques incorporated in MLNDS. With the help of these gauges we have estimated once more some random instrumental errors of measurements from one gauge to another on a level of 2-4% along all diagnostic channels and wavebands of MLNDS. Quite perfect repeatability of measurements during a year was demonstrated on gauges as well. In our experiments under multiple repeated measurements we have evaluated the empirical mathematical expectation "*EME*" (average value) of all registered physical and medical diagnostic parameters, their empirical statistical deviation "σ" and the mean relative random error (dispersion) "δ" of that in percentages:

$$\delta = 100 \cdot \sigma / EME \qquad\qquad (3)$$

Some final statistical results of instantaneous ("snapshot") multiple repeated measurements on the non-alive gauges at laboratory as well as on living objects at clinics (patients of "MONIKI" and healthy volunteers) for LFD and TRO diagnostic methods are presented in Table 1 and Table 2. In a case of TRO technique the analyzed physical parameters were the registered signals from photodiodes in mV in different spectral range (as it is presented in Table 2 – in green, red and infrared wavebands).

As to reproducibility of LFD data (Table 1), we have obtained results of the same order like previously[12]. Some decreasing of a total relative error for each object of investigation we can explain by the more perfect equipment than we had used 10 years ago. Nevertheless, a situation when a random error increases as we go from non-alive gauges to biological tissues has been repeated. The same situation we can see for the TRO diagnostic technique (Table 2). So, this situation is not uniquely for the LFD technique only. Moreover, all calculated medical parameters in TRO have more visible random errors, than LFD ones as well as than all registered physical signals in TRO. It says to us that calculation algorithms in TRO method bring a general deposit in a total error of the method. (We have to note, that the diagnostic

criterion K_f in LFD technique have been specially chosen by us to reduce a total LFD random relative error[12]). General instrumental errors of equipment for both LFD and TRO technique, measured on non-alive gauges, are not very significant and are of the same order (2-4%) like it was established previously.

Table 1. Statistical LFD results of "snapshot" measurements.

Object of investigation	Statistical parameters	Registered physical parameters, arb. un.		Calculated K_f
		I_l	I_f	
Gauges	EME	1918	227,9	0,212
	σ	37,6	9,3	0,007
	δ%	**1,96**	**4,08**	**3,21**
Normal tissue	EME	1207	57,95	0,091
	σ	30,39	4,73	0,006
	δ%	**2,52**	**8,16**	**6,85**
Cancerous tissue	EME	768	341,5	0,621
	σ	35,88	40,13	0,047
	δ%	**4,75**	**11,75**	**7,61**

Table 2. Statistical TRO results of "snapshot" measurements.

Object of investigation	Statistical parameters	Registered physical signals, mV			Calculated medical parameters, rel. un.	
		V_G	V_R	V_{IR}	S_tO_2	V_b
Gauges	EME	897,8	2264	2114	0,89	0,22
	σ	16,23	38,79	24,12	0,04	0,01
	δ%	**1,81**	**1,71**	**1,14**	**4,49**	**4,55**
Normal tissue	EME	821,9	2052	1358	0,81	0,13
	σ	65,71	73,95	47,13	0,09	0,02
	δ%	**7,99**	**3,59**	**3,47**	**11,1**	**15,3**
Cancerous tissue	EME	774,5	2678	1594	0,93	0,16
	σ	39,76	83,18	40,51	0,06	0,01
	δ%	**5,13**	**3,11**	**2,52**	**6,45**	**6,25**

Created gauges are also suitable for the problem of calibration, tuning and metrological testing of both hardware and software components of MLNDS during a manufacture process. In a case of serial production of MLNDS different samples of MLNDS must indicate the same diagnostic data from the same standard gauges. It became possible by variation of attenuation coefficients β in optical unit of MLNDS (see eq. 2) and by variation of special calibration coefficients inculcated into calculation algorithms of MLNDS' software. By this way a metrological platform for further accurate and reproducible clinical measurements can be created.

4. CONCLUSION

In conclusion we have to say that a total ideology of MLNDS turns out to be very effective in a modern medical research. There were previously no such *in vivo* complex tools in hands of medical staff, so a number of new fundamental scientific data are expected to be found out. For example, a direct correlation between levels of chronic hypoxia state in a tested tissue and levels of endogenous accumulation of porphyrins measured by *in vivo* LFD technique was proved recently with the use of MLNDS diagnostic ideology[14]. Now the ideology and construction of MLNDS are protected by both Russian patent No. 2337608, priority since 11.05.2007, and a "PCT" patent application form No. RU2008/000275 (Pub. No. WO/2008/140355, Publication Date 20.11.2008, International Filing Date 05.05.2008). The

equipment is not very expensive, so it is really ready for next manufacturing, state certification, clinical examination, etc. like any excellent and new innovation product.

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