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Metrological Support of Methods and Devices for Noninvasive Medical Spectrophotometry

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The first steps in systematization and analysis of the most fundamental and specific metrological terms, concepts, and definitions applicable to noninvasive medical spectrophotometry (NMS) are discussed. An operational approach to the metrology for the purpose of creation and development of fully functional metrological support of NMS is suggested. Some key properties and aspects of optical in vivo measurements in NMS are discussed. Fabrication of simulation measures and introduction to NMS theory and practice of the notion of diagnostic volume of biological tissues are established as well.

Introduction

Determining vital levels of accumulation of various biochemical substances and their temporal dynamics is a main goal of noninvasive medical spectrophotometry (NMS) [1]. NMS is used to measure the following components of blood and cells: total blood hemoglobin (Hb_t) or tissue hematocrit (Ht_t); volume blood filling (V_b); tissue blood perfusion or microcirculation index (I_m) (microcirculation index is determined using a Doppler method); blood saturation with oxygen (SO_2) in arterial or mixed blood (S_aO_2 or S_tO_2); skin melanin; bilirubin; oil; water, etc. [2-4]. Medical devices monitoring these parameters are called medical diagnostic apparatuses (MDA) [5]. MDA should be provided with adequate metrological support [6-10].

Sources for monitoring systems provide terminology, standardization, calibration, and testing [11-13]. Metrological aspects of monitoring systems have been discussed in the literature in the last 3-5 years (GOST [14]). The first work in this direction is [15]. NMS metrology was discussed in [16]. The foreign literature considers aspects of pulsoximetry and optical tissue oximetry (OTO) metrology [2, 17-19]. General aspects of NMS metrology are beyond the scope of this discussion.

Domestic NMS apparatuses are regarded as indicators rather than MDA devices [9][1]. Various aspects of NMS metrology accuracy involve metrological problems, and NMS therapy requires solution of these problems. The goal of this work was to discuss metrological support of methods and devices for noninvasive medical spectrophotometry and *in vivo* optical methods.

Operational Approach to Classification of Monitoring Systems

Terminology of a monitoring process is a key problem of theoretical metrology [12]. The domestic standardization system is incomplete, thereby making it difficult to evaluate monitoring accuracy. There are two equivalent approaches to this problem: 1) international standards and terms [20]; 2) domestic standards and terms [21]. Monitoring accuracy is regarded differently in these approaches. *Monitoring error* correlated with monitoring accuracy and *uncertainties of measurements* [22]. Any metrological problem requires strict terminology. In our opinion, the *operational approach* is most substantiated [23]. Many metrological terms are empirical. Many metrological terms require definition of operation sequence.

A general measurement scheme by the example of reflection in NMS (Fig. 1) was discussed in [6-10]. NMS

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[1] Indicator devices are diagnostic apparatuses for evaluation of dimensionless parameters and trends.

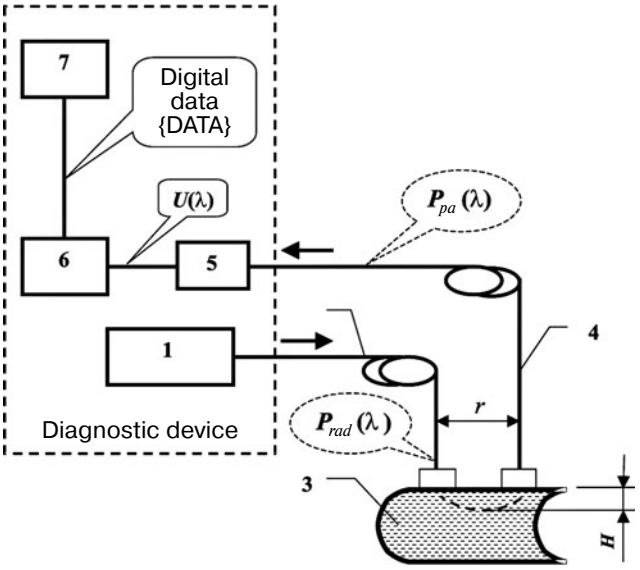

Fig. 1. General measurement scheme by the example of reflection in NMS.

monitoring is often based on reflection measurement [2][2]. In a diagnostic apparatus optical radiation with wavelength λ and power $P_{rad}(\lambda)$ from radiation source 1 is applied to the biological object (BO) 3 using optical system 2 (e.g. optical fiber). The radiation is scattered and partly absorbed in BO components: water, melanin, hemoglobin, etc. A fraction of BO-scattered radiation constitutes backscattering radiation F_{BS}. A fraction of F_{BS} from BO (power, $P_{pa}(\lambda) < P_{rad}(\lambda)$) is applied to detector 5 (PIP). The detector converts $P_{pa}(\lambda)$ into voltage $U(\lambda)$. Electric signal $U(\lambda)$ is amplified and filtered in unit 6, digitized, and applied to computer 7 for mathematical processing. In pulsoximetry the radiation source and detector are attached to the BO. Therefore, systems 2 and 4 are absent without loss of reflection spectrophotometry advances.

Sensors 2 and 4 are attached to the patient's body. Diagnostic information is recorded for 2-3 min. The procedure is repeated for *comparative* analysis. After 1 day, week, month, or another interval of time after therapy, the procedure is repeated for assessing the therapy efficacy.

It was shown in [6] that a BO can be represented as a nonlinear filter. This filter converts $P_{rad}(\lambda)$ into $P_{pa}(\lambda)$. This conversion is equivalent to multiplication by dimensionless function $B(\lambda)$. Function $B(\lambda)$ depends on medical biological parameters (MBP) of the BO. The diffusion equation for semi-infinite medium is an example of function $B(\lambda)$ [2]:

$$B(\lambda) = \frac{z_0 A}{2\pi} \cdot \left[\frac{\mu_d}{r^2 + z_0^2} + \frac{1}{(r^2 + z_0^2)^{3/2}} \right] \times \times \exp\left[-\mu_d (r^2 + z_0^2)^{1/2} \right], \quad (1)$$

where $z_0 = 1/\mu_s'$ is effective length; A is detector area; r is source–detector distance (*base of detection*); $\mu_d = [3\mu_a(\mu_a + \mu_s')]^{1/2}$; $\mu_s' = (1 - g)\,\mu_s$; $g = g(\lambda)$ is anisotropy factor; $\mu_s = \mu_s(\lambda)$ and $\mu_a = \mu_a(\lambda)$ are transport coefficients for scattering and absorption, respectively. Dependence of g, μ_s, and μ_a on MBP is of diagnostic value ($B(\lambda)$ is determined at different wavelengths). Dynamic monitoring of $B(\lambda)$ provides MBP estimate under load tests. An example of $B(\lambda)$ dynamics at different wavelengths in OTO is shown in Fig. 2.

The scheme shown in Fig. 1 provides electric measurement of non-electric parameters [12]. The $B(\lambda)$ function is a *directly measured primary parameter*. The $B(\lambda)$ function is measured in arbitrary units, and the $B(\lambda)$ function is assessed by comparing $P_{pa}(\lambda)$ with reference value $B(\lambda)$. $P_{pa}(\lambda)$ can be measured indirectly using $P_{pa}(\lambda)$ calculated, documented, and stored in the apparatus. The *secondary monitored parameter* is $U(\lambda)$ (output PIP signal). Array $U(\lambda)$ is stored in computer memory as {DATA}. Other parameters (MBP of the BO) are calculated from the {DATA} [7]. NMS implements a classical *indirect method*.

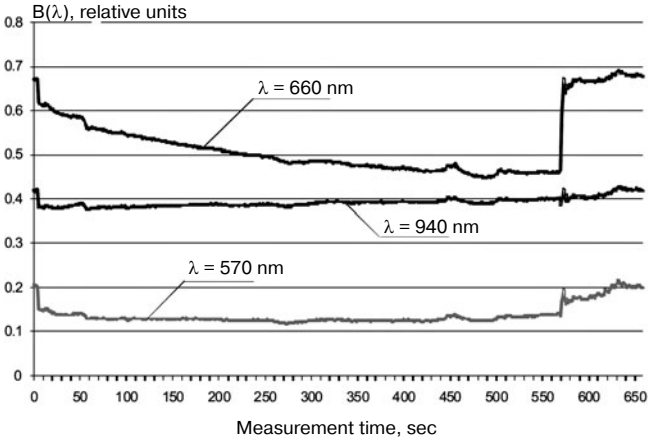

Fig. 2. Example of $B(\lambda)$ dynamics at different wavelength as monitored using a Spectrotest optical oximeter during occlusion test in the patient's finger. The occlusion lasted from 5 to 570 sec.

[2] The reflection process is attributed to an interface. NMS in most diagnostic apparatuses uses back-scattered radiation [16]. In the domestic literature on NMS, the term reflection is used.

The NMS dynamics of $B(\lambda)$, $P_{pa}(\lambda)$, and $U(\lambda)$ *indicates dynamic monitoring*. The MBP in the NMS depends on circulation rate. There are active and passive factors of circulation regulation [4]. These parameters are variable within time interval tenths to hundreds of seconds. Variability of BO parameters is inherent in biomedical systems [13], thereby making it difficult to use the same BO for repeated measurements in NMS.

Data are presented in a NMS in *absolute values*. This is due to recast of indirect *in vivo* parameters of NMS into direct MBP parameters. Hb_t concentration (g/m^3 or mg/l) can be reduced to *effective diagnostic volume* (EDV) used for Hb_t detection (see below). Laser Doppler flowmetry (LDF) faces similar problems. LDF perfusion rate is proportional to erythrocyte volume in the examination zone (Ht_t). LDF examines different blood vessels (capillary, arterioles, venules) [4]. EDV (I_m) is estimated in dimensionless *perfusion units*.

In NMS classical *relative* units are used. Fraction saturation (SO_2) HbO_2 represents relative HbO_2 concentration in blood fractions [14]. Most medical parameters are *related* to reference values. In NMS a pathological focus is compared to a symmetrically placed healthy zone of the human body [13]. This problem is beyond the scope of this work.

Problem of Measuring Accuracy

Metrological support should minimize measuring error [12] and *reduce final uncertainty*. In NMS the following problems should be solved. Effect of the units shown in Fig. 1 on final measuring error and effect of apparatus elements on metrological support (MS) should be considered. In Fig. 1 the measuring error of $U(\lambda)$ is determined by MS of units 5 and 6. Units 5 and 6 are based on LED and ADC with normalized MS. Measuring error of $U(\lambda)$ determines error of MBP in NMS. The units 7 and higher have no effect on final diagnosis and require only digital attestation[3] [24]. The NMS error is determined by metrological support of units 1-5.

Instrumental error of biomedical tests is due to *interaction of the BO with the apparatus*. In NMS tissue heating and temperature drift of biological tissue cause this error. This component of instrumental error is called the *interactive component of error*. In NMS the *interactive component of error* is significant.

It is difficult to estimate error components in NMS. There are absolute, relative, and reduced errors [12]. Absolute error is the difference between measured (X_{meas}) and actual (X_{act}) values of a monitored parameter. Relative error is ratio X_{meas}/X_{act}. X_{act} is determined experimentally or theoretically[4]. Theoretical calculation of a patient's parameters is impossible. In NMS the patient's parameters should be determined experimentally using available apparatuses.

Error in S_tO_2 is considered as an example. SO_2 is measured for 20-30 sec with stress load on a blood vessel. S_tO_2 is assessed in NMS *in vivo* and averaged over the examined zone. It is difficult to measure true value of S_tO_2.

Theoretical estimates of MBP in the norm and various load tests avoid this problem. In OTO and LDF, respiration tests and arterial occlusion tests with temperature variation can be used [4]. These tests provide calibration in NMS in MBP units [4, 25]. Testing methods based on human materials are prohibited [14]. This makes it difficult to implement final tests in NMS.

Simulation Methods of Calibration and Graduation of Apparatuses

BO simulators are an alternative to human tissue. In NMS $B(\lambda)$ living tissue is equivalent to $B(\lambda)$ of a non-biological object [27]. This provides a methodological basis for *optical phantoms of BO* [2, 19]. Such phantoms are *working simulation media* (WSM). WSM provide $B(\lambda)$ of MBP of a BO in norm and pathology [26, 27]. In this work the term simulation is applied to the theory.

This term provides the difference between biological and natural WSM. Each WSM correlates with $B(\lambda)$ function. This provides a methodological approach to calibration of NMS apparatuses and verification of measuring error reproducibility. These methods require state certification and standardization for NMS of MBP.

Spectrotest oximetry tests shown in Fig. 3 are an example of WSM in NMS [27]. Fluoroplastic FT-4 (GOST 14906-77) is used in these tests. This material is chemically resistant, which makes it appropriate for WSM. Light scattering in the BO is simulated using polymeric films with different absorption, scattering and fluorescence properties for NMS.

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[3] Systematic error is due to the calculation algorithm. Improving models and algorithms can reduce this error. In NMS specific simple models should be used. Digital attestation is used to verify models.

[4] In the literature X_{act} is sometimes defined as true value of the monitored parameter. True value of a monitored parameter should be used in theoretical research only [20]. Experimental value close to theoretical value should be used in practice. It is very difficult to obtain this value [20].

Effective Diagnostic Volume

Quantitative detection of chemical substances in tissues requires evaluation of *effective diagnostic volume* (EDV) of the BO. EDV generates useful diagnostic signal $P_{pa}(\lambda)$. EDV of pathological tissue is changed because of modification of optical properties. In the general case EDV of pathological tissue differs from EDF of normal tissue. EDV in NMS practice should be evaluated as accurately as possible.

In the literature the term EDV is not defined strictly. In [9] the term EDV is defined as *effective volume in examination zone for P_{min} at level 75-95% total power of BO radiation* (0.75 ($P_{0.75}$); 0.95 ($P_{0.95}$), etc.). This definition provides quantitative estimate of EDV. Let us consider the problem of one-dimensional radiation propagation in biological tissues (Fig. 1). Effective depth H is determined by μ_a, μ_s, μ_ρ in the medium [8]. In NMC $P_{BSmin}(H)$ is γ = 0.9-0.95 of $F_{BS}(\infty)$:

$$P_{BSmin}(H) = \gamma \cdot F_{BS}(\infty), \qquad (2)$$

where $F_{BS}(\infty)$ is power of back-scattered radiation in semi-indefinite medium.

At $\mu_a = 0$ and ($F_0 = 1$) equations derived in [16] are valid

$$F_{BS}(\infty) = F_0 = 1;\ \mu_s = R\mu_\rho/(1 - R), \qquad (3)$$

where R is reflection coefficient in the BO. $P_{BSmin}(H)$ is:

$$P_{BSmin}(H) = F_0\mu_s H/(1 + \mu_s H). \qquad (4)$$

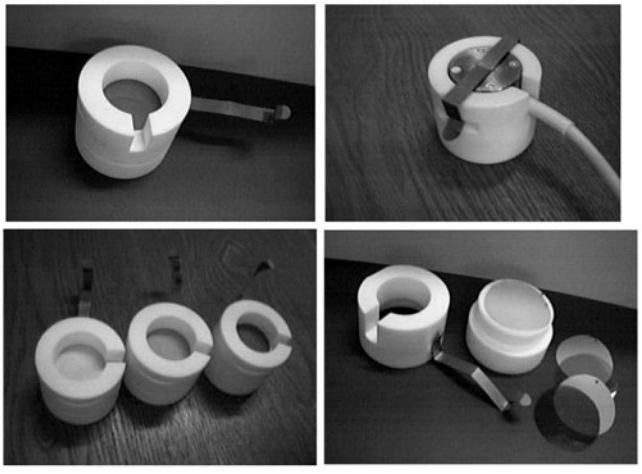

Fig. 3. General view and structure of simulation appliance for calibration and graduation of the Spectrotest oximeter.

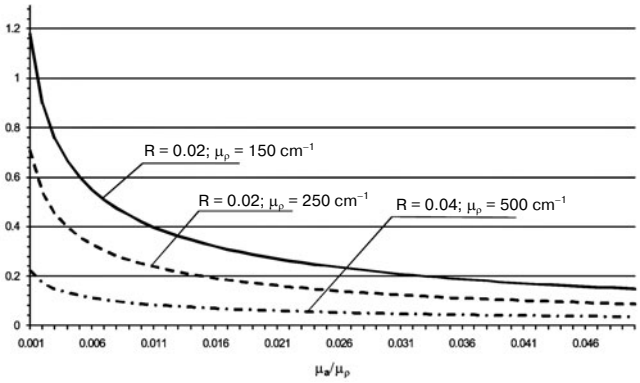

Fig. 4. H estimate in one-dimensional system with multiple scattering and absorption in a BO.

Combination of Eqs. (2), (3), and (4) gives:

$$H = \gamma/\mu_s(1 - \gamma). \qquad (5)$$

At typical values of R (0.02-0.05), μ_ρ (50-1000 cm^{-1}), and μ_s (1-55 cm^{-1}) the effective value of H is 0.16-19.0 cm. μ_s depends on radiation wavelength λ. In the general case EDV depends on λ.

EDV decreases upon radiation absorption. It was demonstrated in [8] that H (EDV in one-dimensional model) is:

$$H = \frac{1}{2\alpha} \cdot \ln\left[\frac{\alpha(1+\gamma)/(1-\gamma)+\beta_1}{\alpha+\beta_1}\right], \qquad (6)$$

where

$$\alpha = \sqrt{\beta_1^2 - \beta_2^2};$$

$$\beta_1 = \omega \cdot \frac{\mu_a - \mu_\rho \ln(1-R) + \mu_\rho \ln(1-\omega+\sqrt{\omega^2 - R^2 e^{-2\mu_a/\mu_\rho}})}{\sqrt{\omega^2 - R^2 e^{-2\mu_a/\mu_\rho}}};$$

$$\beta_2 = R \cdot e^{-\mu_a/\mu_\rho} \times$$

$$\times \frac{\mu_a - \mu_\rho \ln(1-R) + \mu_\rho \ln(1-\omega+\sqrt{\omega^2 - R^2 e^{-2\mu_a/\mu_\rho}})}{\sqrt{\omega^2 - R^2 e^{-2\mu_a/\mu_\rho}}};$$

$$\omega = \frac{1-(1-2R)\cdot e^{-2\mu_a/\mu_\rho}}{2}.$$

EDV can be calculated numerically. H curves calculated from Eq. (6) as functions of R, μ_a, and μ_ρ at $\gamma = 0.95$ are shown in Fig. 4. Typical values of H are 1-8 mm. EDV inversely depends on BO scattering and is proportional to

BO absorption. EDV also depends on *r* (Fig. 1) determining MS of the NMS apparatus.

Conclusion

Four groups of methods constitute metrological support of NMS.

1. Reproducible and standard methods of tuning, calibration, and verification of NMS apparatuses without use of human materials.

2. Evaluation of instrumental and methodological errors of NMS apparatuses.

3. Research into EDV in NMS; theoretical and experimental evaluation of EDV effect on metrological parameters of NMS apparatuses.

4. Unification of diagnostic methods for practical medicine of various diseases of different nosology and standardization of combined methods of medical information in NMS and development of integral diagnostic algorithms. NMS standardization requires combined solution of the four problems.

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