Spectral Control by Light Interaction with Soft Biological Tissues for Light-Therapy Purposes

Vladimir V. BARUN[1,2] and Arkady P. IVANOV[1]
[1]B.I. Stepanov Institute of Physics, Belarus National Academy of Sciences, Nezavisimosti Pr. 68, Minsk 220072, Belarus
[2]Belarus State University of Informatics and Radioelectronics, Brovka Str. 6, Minsk 220013, Belarus
barun@dragon.bas-net.by

***Abstract* — A review of authors-designed techniques for increasing light power, absorbed by various tissue chromophores, via the optimal selection of the wavelength irradiating skin surface is given. The techniques are based on the simulation of light transfer through biotissues with accounting for the optical tissue model in the wavelength range of 300 to 1000 nm. Light-oxygen and photodynamic effects as well as photodissociation of blood oxyhemoglobin are considered as the subjects of the optimization. It enables the absorbed light power to be increased up to several times by the proper choice of the wavelength. These photo-induced mechanisms of the light action are widely used for various non-invasive light-therapy methods, so that the proposed spectral control algorithms tissues can be easily implemented in various fields of practical medicine.**

***Index Terms* — biological tissues, skin, light-oxygen effect, photodynamic therapy, oxyhemoglobin photodissociation.**

I. INTRODUCTION

There are known various mechanisms of light action on biotissues related with light absorption. This paper considers three such mechanisms, namely the light-oxygen (LOE) and photodynamic effects (PDE) as well as the photodissociation of blood oxyhemoglobin. All these mechanisms are or can be used in different kinds of light therapy treatments of a human organism. Their efficiencies are proportional to the light power absorbed by a target chromophore in tissue. These targets are, respectively, dissolved molecular oxygen for the light-oxygen mechanism, a photosensitizer for the photodynamic action, and oxyhemoglobin for the photodissociation. The purpose of this paper is to maximize the absorbed light power by a suitable choice of a wavelength irradiating the skin surface. In succeeding so, one can optimize the non-invasive light therapy procedures. In other words, the desired maximization will enable one to utilize less irradiation power for achieving the same therapeutic effect or to achieve more positive effect for the same irradiation power.

The idea of the optimization is rather simple. Really, optical properties of soft biotissues, especially their absorption coefficients, are spectrally selective, so that the tissue acts as a spectral filter with complex transmittance. The light power absorbed by a target chromophore at specific depth z is proportional to the product of the fluence rate at this depth by the absorption coefficient of the chromophore. By varying the irradiation wavelength, one can change the filter transmittance and, hence, the fluence rate to maximize the said product. It is obvious that the optimal wavelength does not necessarily coincide with the maximum of the absorption coefficient. The below results are obtained by using the optical tissue model [1] and the analytic techniques [2] for describing radiative transfer though multilayered human skin.

II. LIGHT-OXYGEN EFFECT

The effect is the spectrally-selective absorption of optical photons by molecular oxygen O_2 dissolved in tissue to initiate electronic transitions of O_2 molecule from the ground triplet state to singlet ones. The so-formed singlet oxygen activates the biological system. The LOE was discovered [3] by direct measurements of the spectral light action on erythrocytes. It is used for light therapy of various pathologies of a human organism, including oncologic diseases [3]. The amount of singlet oxygen produced per unit irradiation time due to the LOE is proportional to the light power absorbed by O_2. The larger this amount, the more noticeable the effect. However the delivery of large light power to a desired tissue site in its depth is problematic. Biotissue is known to be a strongly light scattering and absorbing medium to substantially attenuate the incident radiation flux. The light penetration depth in tissue varies from a fraction of to several millimeters as a function of wavelength λ [4]. The increase in the irradiating power provides the proportional increase in the absorbed power, but leads also to some undesirable consequences, e.g. to excessive heating of healthy tissue portions, their possible coagulation, and following damage. Besides, the additional energy is uselessly wasted.

There are known five absorption bands of dissolved O_2 in the visible and near-infrared ranges [3]. Consider the band centered near λ_{max} = 586 nm. Introduce differential (at specific depth z) O_2-absorbed power

$$w_{O_2}(\lambda, z) = f_{O_2}\mu_{O_2}(\lambda)E(\lambda, z), \quad (1)$$

where f_{O_2} is the O_2 volume fraction; $\mu_{O_2}(\lambda)$ is the O_2 spectral absorption coefficient; $E(\lambda, z)$ is the fluence rate at depth z. Similarly, introduce integral O_2-absorbed power characterizing the total absorption by tissue slab $z_1 \div Z_1$

$$W(\lambda) = \int_{z_1}^{Z_1} w(\lambda, z)dz / (Z_1 - z_1)\,, \qquad (2)$$

where $Z_1 \approx 8$ mm is the depth of the fat layer.

Figure 1 illustrates differential w^* (*a*) and integral W^* (*b*) spectral absorbed power values. Quantities w^* and W^* are the ratios of functions of Eqs. (1) and (2) to the respective quantity at wavelength λ_{max}. One can see from Fig. 1 that in deep dermis layers at z, $z_1 \geq 1.5$ mm there can be substantial increase (up to several times) in the absorbed power under skin irradiation at a shifted wavelength λ as compared with the irradiation at λ_{max}. On the base of these results, there was proposed a method [5] of laser therapy of skin surface and deep dermis layers comprising the irradiation of skin surface at a wavelength shifted by 5 to 8 nm to the red spectral range with respect to λ_{max}.

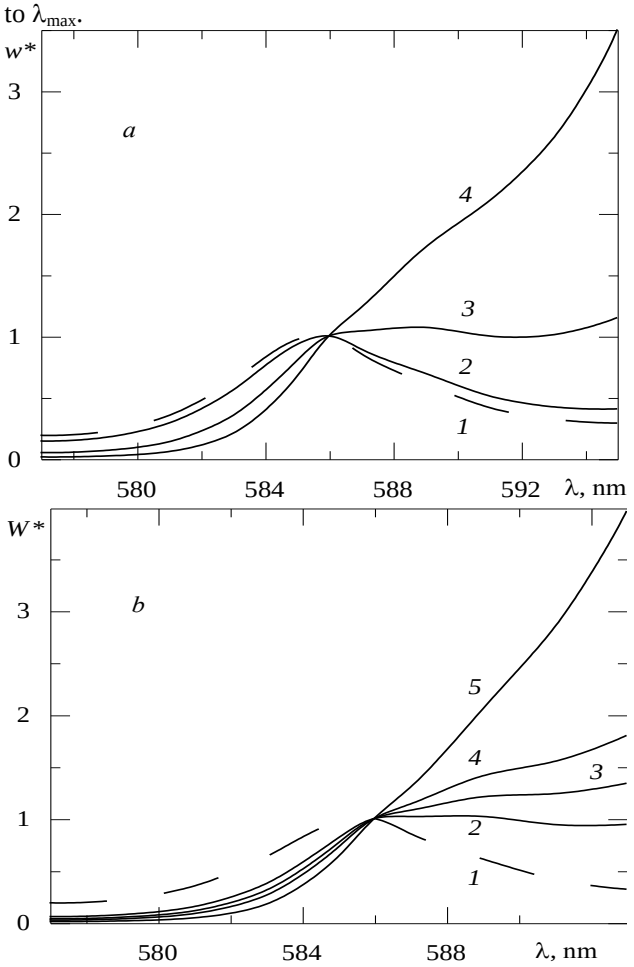

Fig. 1. Spectral O_2-absorbed power values w^* (*a*) and W^* (*b*) (curve *1* is the O_2-absorption band) for (*a*) z = 0.3 (curve *2*), 1.5 (*3*), 3 mm (*4*) and (*b*) z_1 = 1 (*2*), 1.5 (*3*), 2 (*4*), and 3 mm (*5*)

III. PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) is currently successfully used for treating various diseases, including oncologic ones. The standard PDT procedure comprises, in general, injecting a photosensitizer (PS) intravenously and irradiating a tumor site by light, the wavelength of which coincides with the maximal PS absorption.

The physical mechanism of PDT can be schematically represented as follows. After the PS injection, it is usually concentrated in tumor tissues. The irradiation excites PS molecules to a higher energy level. The energy is transferred from the excited PS to oxygen molecules, which are always present in tissue. Oxygen moves from its usual triplet state to the singlet one. The singlet oxygen is toxic for biotissue to damage it and to finally leat to tumor necrosis. The preferred PS localization in tumor provides high selectivity of the irradiation, so that healthy tissue surrounding the tumor is hardly subjected to the light action.

There are known various PSs. Typical groups of such substances are porphyrins, porphycenes, and phthalocyanines. All of them have intense absorption bands in the near UV – blue and red spectral ranges at wavelengths, respectively, 350 to 420 nm and 600 to 700 nm. Under PDT of subsurface tumor regions, one usually uses the red region due to the much higher light penetration depth with λ = 600 to 700 nm as compared with the blue range.

One of the main PDT problems is to deliver required light power to a tumor site owing to biotissue strongly scatters and absorbs light. The PDE of the irradiation can be only achieved at a specific fluence rate being absorbed by a tumor. If a PS absorbs less power, there are small amount of singlet oxygen formed to give PDT low efficiency.

A PDT technique is known [6] to comprise the irradiation of a tumor containing PS "Photosense" at two wavelengths λ_1 and λ_2. The first one λ_1 = 675 nm corresponding to the maximal PS absorption is designated for the destruction of upper tumor layers and the second one damages the lower layers. The essence of the technique is the larger penetration depth of light at λ_2 than at λ_1. The latter is highly attenuated by a tumor owing to the PS. The attenuation of light at λ_2 is weaker due to it falls on the wing of the PS absorption band. The drawback of this technique will be illustrated below.

Consider here a case of tumor localization in dermis, where blood vessels are. After the PS injection, spectral values $\mu(\lambda)$ of the tumor absorption coefficient change. Quantity $\mu(\lambda)$ can be calculated as follows:

$$\mu(\lambda) = \mu_{ps}(\lambda) + \mu_b(\lambda) + \mu_t(\lambda) \qquad (3)$$

where $\mu_{ps}(\lambda)$, $\mu_b(\lambda)$, and $\mu_t(\lambda)$ are the spectral absorption coefficients of PS, blood, and bloodless tissue, respectively.

The maximal increase in $\mu(\lambda)$ is obviously to occur at the maximal PS absorption at $\lambda = \lambda_{max}$. Therefore, light at λ_{max} is noticeably attenuated than light at the wings of the PS absorption band. The power absorbed by a PS in a unit tumor volume is of the form

$$W_{ps}(\lambda, z) = f_{ps}\mu_{ps}(\lambda)E(\lambda, z) / E_0(\lambda), \qquad (4)$$

where f_{ps} is the PS volume fraction, $E(\lambda, z)$ and $E_0(\lambda)$ are the fluence rate at depth z and incident on skin surface.

It is seen from Eq. (4) that the absorbed power depends on the product of $\mu_{ps}(\lambda)E(\lambda, z)$. When one shifts the irradiation wavelength by $\Delta\lambda$ with respect to λ_{max} toward both the red and blue wings, coefficient $\mu_{ps}(\lambda)$ decreases, but fluence rate $E(\lambda, z)$ grows. Hence, product $\mu_{ps}(\lambda)E(\lambda, z)$ can either increase or decrease. While it increases, the required higher efficiency of PDT is achieved.

As noted above, the subsurface tumor is usually irradiated at a wavelength of 600 to 700 nm, because an

essentially larger light penetration depth here as compared with the blue – green range. General considerations on spectral tissue characteristics show that the said shift should be to the red wing of the PS absorption band. Really, at a wavelength of 600 to 700 nm the absorption coefficient of blood with typical oxygen saturation $S > 0.5$ (the ratio of oxyhemoglobin concentration to the total hemoglobin) decreases in the red end. Consequently, the wavelength shift to longer λ (to the red) provides more increase in $E(\lambda,z)$ and, as a result, to an enhanced absorbed light power as compared with the opposite shift. The additional increase in $E(\lambda,z)$ is achieved by decreasing absorption coefficient of melanin (epidermis component) in the red. Calculations, shown in Fig. 2, of the absorbed power of typical PSs have shown that the decrease in the irradiation wavelength with respect to λ_{max} leads to lower values $W_{ps}(\lambda)$ as compared with the irradiation at λ_{max}. Therefore, the wavelength shift has to be in the red end.

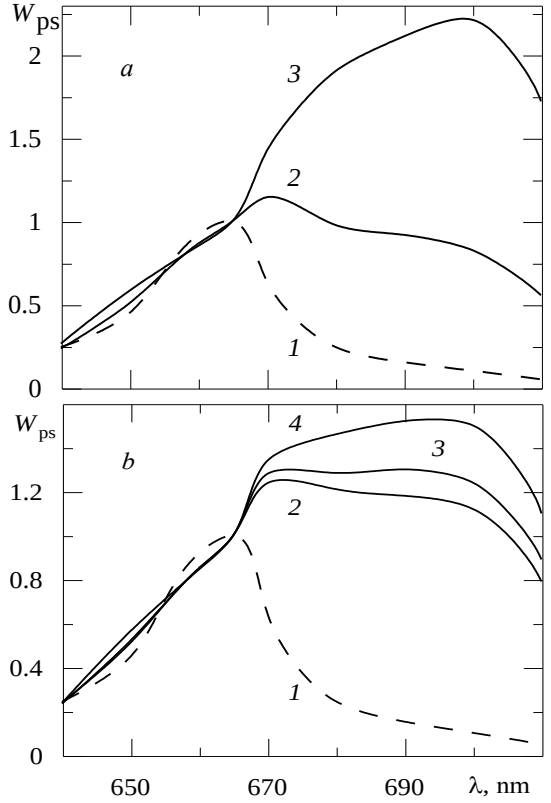

Fig. 2. Normalized absorption spectrum of PS "Fotolon" (curve *1*) and normalized power absorbed by the PS at (*a*) $S = 0.75$, blood vessel volume fraction $C_V = 0.04$ (*2*) and 0.08 (*3*), (*b*) $C_V = 0.04$, $S = 0.75$ (*2*), 0.9 (*3*), and 0.97 (*4*)

Consider typical PS "Fotolon"(on the base of chlorine e6) widely used for PDT [7]. Its absorption spectrum $\mu_{ps}(\lambda)$ was measured [7] as a difference of the respective coefficients of blood containing the PS and before the PS injection. These data normalized by $\mu_{ps}(\lambda_{max})$ are shown by dashed curve *1* in Fig. 2. The maximal absorption is seen to correspond $\lambda_{max} = 665$ nm. Fig. 2 illustrates also spectral power $W_{ps}(\lambda,z)$ absorbed by the PS (curves *2* to *4*). These values are normalized similarly to $\mu_{ps}(\lambda)$, namely to $W_{ps}(\lambda_{max},z)$. Fig. 2*a* corresponds to constant S and varying C_V, but Fig. 2*b* does to constant C_V and varying S. The absorbed power was calculated according to [2].

The calculations have shown that the so-normalized values of $W_{ps}(\lambda,z)$ depend weakly on melanin concentration and on depth z for 1 mm < z < 4 mm. One can see from Fig. 2 that the irradiation wavelength shift to the red end respective to λ_{max} provides the increase in the PS absorbed power to give rise to the enhanced PDT efficiency. With using the said shift, the increase in $W_{ps}(\lambda,z)$ as compared with the irradiation at λ_{max} can be twofold or more. The data in Fig. 2 tells that the first wavelength of [6] is utilized ineffectively and the achieved result, namely the increase in the PS absorbed power of [6] and, hence, the higher concentration of singlet oxygen, is provided apparently by the second wavelength only.

The shift values $\Delta\lambda$ and the maximal gain w_0 in absorbed power $W_{ps}(\lambda,z)$ are shown in Fig. 3. Value w_0 is meant as ratio $W_{ps}(\lambda_{max} + \Delta\lambda,z)/W_{ps}(\lambda_{max},z)$, where wavelength $\lambda_{max} + \Delta\lambda$ correspond to maximal $W_{ps}(\lambda,z)$, to give the increase in the PS absorbed power under irradiation at the shifted wavelength as compared with the irradiation at λ_{max}. One can see from Fig. 3 that the values of $\Delta\lambda$ and w_0 increase essentially for tissues with large volume fractions C_V of blood vessels and high oxygen saturation S. Note that according to model [8] $C_V \cong 0.06$ and $S > 0.75$ for arterial blood. Fig. 2 tells also that the wavelength shift to the blue – green end leads to the decrease in PS absorbed power as compared with the irradiation at λ_{max} .

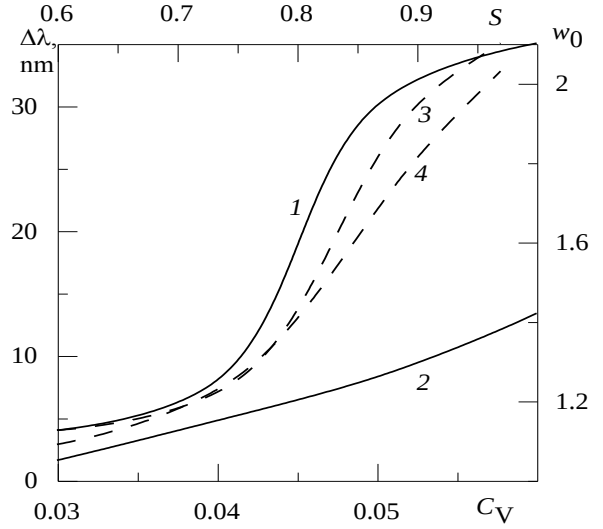

Fig. 3. Functions $\Delta\lambda(C_V)$ (curve *1*, lower abscissa scale, left ordinate scale), $w_0(C_V)$ (*2*, right ordinate scale) for $S = 0.75$ and $\Delta\lambda(S)$ (*3*, upper abscissa scale), $w_0(S)$ (*4*) for $C_V = 0.05$

The illustrated example shows that one can achieve the enhancing in PDT efficiency by 5 to 100 % due to the irradiation wavelength shift by $\Delta\lambda = 5 – 30$ nm, the said shift depending on C_V and S. The particular values of C_V и S can be retrieved by the spectrophotometric method [9]. According to the results of this Section, there were get two Patents The proposed techniques comprise the PDT method [10] and the irradiation method during PDT [11].

IV. OXYHEMOGLOBIN PHOTODISSOCIATION

Local generation of molecular oxygen. It was experimentally discovered [12] that under biotissue irradiation by light with frequency ν (or with wavelength $\lambda = c/\nu$, where c is the light velocity in the medium) there occurred photodissociation of oxyhemoglobin HbO_2 that, after the absorption, decomposed to deoxyhemoglobin and molecular oxygen. Quantum yield q of the process (the ratio of the number of the formed O_2 molecules to the number of the absorbed photons) was studied, for example [13], by the laser kinetic spectroscopy method. It was shown that, under the excitation by the UV – visible light with $\lambda \cong 350 – 650$ nm, q values were approximately constant to be 3 to 5 % as a function of the temperature and some other factors. There was proposed [14] a hypothesis that this mechanism can be responsible for biologic action of light on tissues. It is understood that the photodissociation efficiency is proportional to the light power absorbed by HbO_2 in tissue.

Introduce the concept of differential photodissociation efficiency (DPE) that is the number $n(z,\lambda)$ of oxygen molecules formed during unit time in unit tissue volume at depth z under skin surface irradiation by unit monochromatic power density:

$$n(z,\lambda) = \frac{\mu_a(\lambda) H f C_v(z) S \lambda q E(z,\lambda)}{hc}. \qquad (5)$$

Here $\mu_a(\lambda)$ is the HbO_2 spectral absorption coefficient, H = 0.4 [8] is the hematocrit (volume fraction of erythrocytes in blood), f = 0.25 is the volume fraction of hemoglobin in an erythrocyte, $h = 6.63 \cdot 10^{-34}$ J·s is the Plank constant.

Consider ratio

$$r(z, \lambda_1, \lambda) = n(z, \lambda_1)/n(z, \lambda) \qquad (6)$$

giving the increase (or decrease) in DPE at a specific depth z during the skin irradiation at wavelength λ_1 as compared with the irradiation at λ.

Equations (5) and (6) correspond to the monochromatic irradiation. If one uses a light beam over spectral range Δλ to generate molecular oxygen, then Eq. (6) takes the form

$$r^*(z, \lambda_1, \lambda) = \int_{\Delta\lambda_1} n(z, \lambda_1) d\lambda_1 \Big/ \int_{\Delta\lambda} n(z, \lambda) d\lambda . \qquad (7)$$

Figure 4*a* illustrates the depth structure of the DPE at wavelengths 418 (curves *1*), 575 (*2*), 585 (*3*), 600 (*4*), and 632 nm (*5*). These data are given for melanin concentration f_m = 0.04, stratum corneum and epidermis thicknesses d_s = 20 μm and d_e = 100 μm, C_v = 0.04, and S = 0.75. Power density irradiating the skin surface is E_0 = 1 W/cm^2. One can see from Fig. 4*a* that different wavelengths are the most effective for oxygen generation at various depths. In the upper dermis layers, blue light with λ = 418 nm induces the maximal HbO_2 photodissociation. As z increases, the most effective wavelengths move sequentially to the red spectral region, being λ= 575 nm for 0.22 mm ≤ z ≤ 0.9 mm, λ= 585 nm for 0.9 mm ≤ z ≤ 2.5 mm, and λ= 600 nm for z ≥ 2.5 mm. The boundaries of these depths are shown in Fig. 4*a* by the vertical dashed lines. The calculations (not given in Figures) for other structural and biophysical parameters of tissue [4] changing within ranges of 15 μm ≤ d_s ≤ 25 μm, 0.02 ≤ f_m ≤ 0.08, 60 μm ≤ d_e ≤ 120 μm, 0.02 ≤ C_v ≤ 0.06, and 0.5 ≤ S ≤ 0.97, as well as for the irradiation within spectral band Δλ = ± 5 nm respectively to λ have showed that the boundary positions, where one or another wavelength is the most effective, are stable to the changes in d_s, f_m, d_e, C_v, and S. For example, the said depth values vary within very narrow limits of 0.22 ± 0.02, 0.9 ± 0.05, and 2.5 ± 0.1 mm. This enables one to utilize the said wavelengths of 418, 575, 585, and 600 nm for the most effective generation of the molecular oxygen within the above depth intervals.

Figure 4*b* shows ratio r as a function of depth for the case of λ_1 = 575 nm. These data enables the quantitative comparison of the PDE values under the irradiation by 418, 575, 585, and 600 nm to induce the oxyhemoglobin photodissociation and to enhance the molecular oxygen concentration at the corresponding depths in dermis.

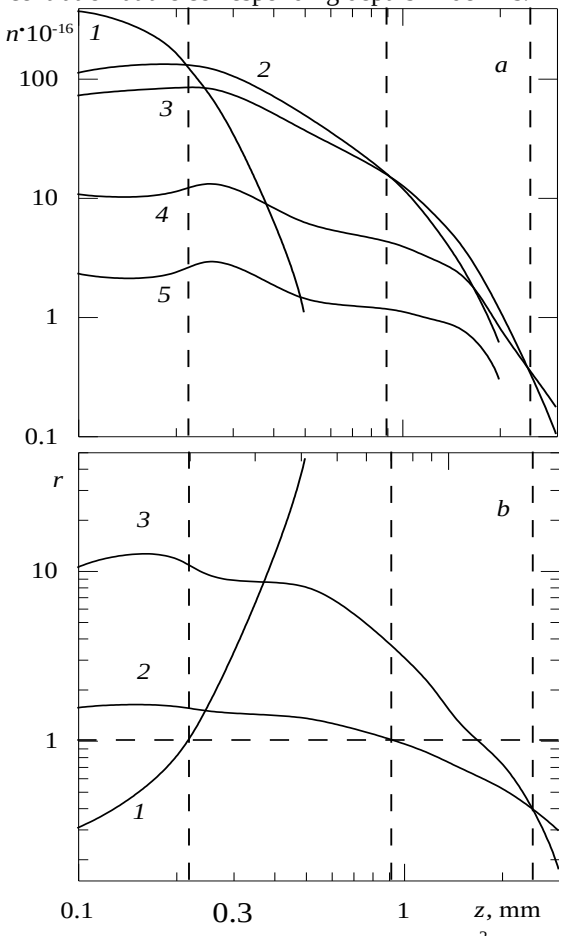

Fig. 4. Depth dependences of (*a*) DPE, W/(cm^{3}s) for λ = 418 (*1*), 575 (*2*), 585 (*3*) 600 (*4*), and 632.8 nm (*5*) and (*b*) ratio r for λ_1 = 575 nm and λ = 418 nm (*1*), λ_1 = 575 nm and λ = 585 nm (*2*), λ_1 = 575 nm and λ = 600 nm (*3*)

The above data have constituted the base for a method [15] of local enhancing the concentration of molecular oxygen in skin dermis comprising the irradiation of skin surface by a light beam to induce photodissociation of oxyhemoglobin and featuring in that one preliminary determines the depth of a pathological region in dermis and, for the depth less than 0.22 mm, makes the irradiation at wavelength 418 ± 5 nm, for the depth from 0.22 to 0.9 mm does at 575 ± 5 nm, for the depth from 0.9 to 2.5 mm does at 585 ± 5 nm, and for the depth larger than 2.5 mm does at 600 ± 5 nm.

Integral generation of molecular oxygen. Introduce the concept of integral photodissociation efficiency (IPE) that is the number $N(\lambda)$ of oxygen molecules formed during unit time in the whole dermis layer under skin surface irradiation by unit monochromatic power density:

$$N(\lambda) = \frac{\mu_a(\lambda) HfS\lambda q}{hc} \int_{z_0}^{\infty} C_V(z) E(z,\lambda) dz \,. \qquad (8)$$

Here z_0 is the depth of the irradiated dermis surface. Quantity $N(\lambda)$ has dimension $cm^{-2}s^{-1}$. The upper integration limit in Eq. (8) is set to ∞ for the simplicity, because the fluence rate in deep dermis layers is negligible.

Consider ratio

$$R(\lambda_1, \lambda) = N(\lambda_1)/N(\lambda) \qquad (9)$$

giving the increase (or decrease) in IPE within the whole dermis layer during the skin irradiation at wavelength λ_1 as compared with the irradiation at λ.

Equations (8) and (9) correspond to the monochromatic irradiation. If one uses a light beam over spectral range $\Delta\lambda$ to generate molecular oxygen, then Eq. (5) takes the form

$$R^*(\lambda_1, \lambda) = \int_{\Delta\lambda_1} N(\lambda_1) d\lambda_1 \Big/ \int_{\Delta\lambda} N(\lambda) d\lambda \,. \qquad (10)$$

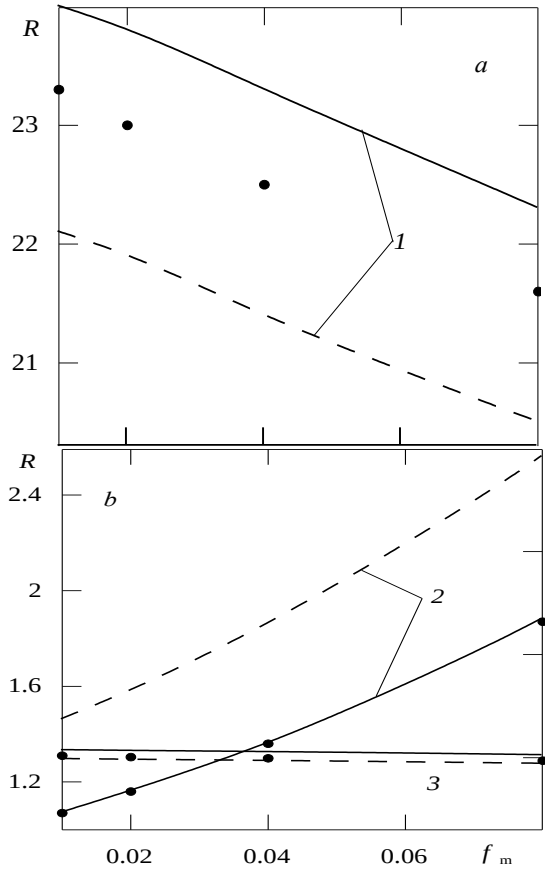

Fig. 5. Ratio R as a function of melanin volume fraction in epidermis under monochromatic irradiation of skin surface at λ_1 = 575 nm and λ = 632.8 nm (curves *1*), 418 (*2*), and 585 nm (*3*), C_V = 0.04 (solid) and 0.08 (dashed curves), S = 0.75. The symbols are the similar ratio R^* for irradiation at, respectively, 575 ± 5 nm, 632.8 ± 5 nm, 418 ± 5 nm, and 585 ± 5 nm at C_V = 0.04

A method [16] for non-invasive generation of molecular oxygen in the dermis layer is known to comprise the skin irradiation at wavelength λ = 632.8 nm with simultaneous tissue heating to temperature about 42° C. It is show in Fig. 5*a* that the drawback of this method is a small amount of the so-formed O_2 molecules owing to using λ=632.8 nm. One can see from Fig. 5*a* that the irradiation at λ_1 = 575 nm provides the much more IPE as compared with known λ = 632.8 nm. The IPE increases up to 20 to 25 times.

We have found that the irradiation of skin surface at wavelength 575 nm provides the maximal IPE values as compared with other λ in the near UV – visible range. To illustrate this, Fig. 5*b* compares R and R^* for λ_1 = 575 and λ = 418 (curves *2*), λ_1 = 575 nm and λ = 585 нм (*3*).

Wavelength 418 nm corresponds to the maximal oxyhemoglobin absorption and 585 nm is recommended in [16] as a wavelength providing the maximal effective HbO_2 absorption coefficient proportional to product $\mu_a(\lambda)E(z,\lambda)$. One can conclude from Fig. 5*b* that the increase in IPE under the irradiation at 575 nm is about 1.1 to 2.5 times with respect to λ = 418 и 585 nm. Note that rather small IPE quantities of $R(\lambda)$ (approximately 1.1 to 1.2) at λ = 418 nm occur for low $f_m \le 0.02$ values typical for pathological vitiligo skin [4] and, therefore, they are not representative.

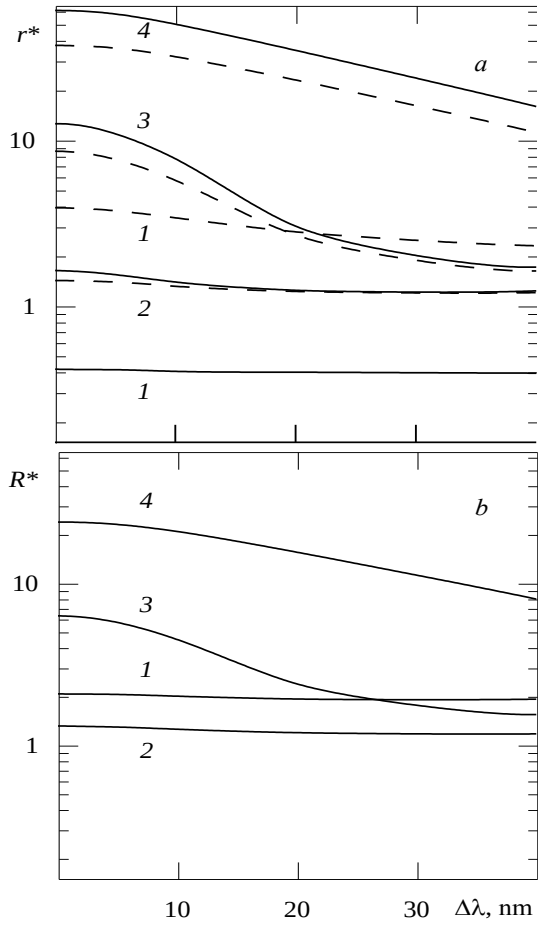

Fig. 6. Dependence of r^* at z = 0.12 (solid curves) and 0.3 mm (dashed) (*a*) and of R^* (*b*) on halfwidth $\Delta\lambda$ of the irradiation spectrum for λ_1 = 575 nm and λ = 418 nm (*1*), 585 nm (*2*), 600 nm (*3*), and 632.8 nm (*4*); f_m = 0.08, d_1 = 20 μm, d_2 = 100 μm, C_v = 0.04, S = 0.75

There arises a question, how does the DPE and IPE change while $\Delta\lambda_1$ and $\Delta\lambda$ vary. For comparison, let $\Delta\lambda = \Delta\lambda_1$ to provide the irradiation at the same spectral power density. Fig. 6 [17] gives ratios r^* at two depths (*a*) and R^* (*b*) on $\Delta\lambda$. Wavelength 575 nm was taken as λ_1. One can see that the both DPE and IPE decrease as a whole, when $\Delta\lambda$ grows. It is understood, because the features in spectral optical characteristics of tissue are smoothed away and averaged over wider interval $\Delta\lambda$. Therefore, it is preferable to use laser irradiation for inducing the photodissociation, sine it provides more spectral power and more noticeable increase in O_2 generation. This fact is especially essential for λ = 600 and 632 nm.

On the base of the above results there was proposed a method [18] of enhancing the O_2 concentration in the whole depth of skin dermis comprising the irradiation of skin surface by a light beam with wavelength λ=575±5 nm.

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