Мікросистеми та фізична електроніка

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Control of Optical Clearing of Human Skin by Ellipsoidal Reflector Method

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***Abstract*—Current research deals with the problem of optical clearing during photometry by ellipsoidal reflectors. The specific problem is optical clearing of human skin, specifically the level control tasks during non-invasive conditions of experiment. In silico experiment involve Monte Carlo simulation of light propagation in multi-layered biological tissue and ellipsoidal reflector. The research was made for the set of human skin layers optical properties and their anatomic thicknesses. There were received photometric images in back scattered light for human skin from following parts of body: palm (hand), chest, abdomen, shoulder, back and thigh. Based on the zone analysis there were received illuminance dependencies of middle and external rings of photometric images from the optical clearing time. In addition, there was investigated the influence of optical clearing time on the character of light scattering on human skin from different parts of human body.**

Ref. 45, fig. 5, tabl. 2.

Keywords* — *optical clearing, ellipsoidal reflector, human skin, photometric image.

I. INTRODUCTION

Optical and laser methods of diagnostic and therapy rapidly develops in medical technologies. Due to the constructive variety and wide spectral range, they can solve various tasks in ophthalmology, stomatology, oncology, cosmetology, and other branches. Use of lasers as the optical scalpels and tweezers in oncology allow to remove malignant neoplasms with high ablation level [1]–[3]. At the same time, it prevents cancer cells from penetration into the surrounding healthy ones. During the excimer laser correction and photorefractive keratectomy [4], the technology allows to change the cornea shape and to restore the effective focusing of rays on the retina. Low-intensity laser radiation with therapeutic purposes applies also for rugosity smoothing, cellulite treatment, hair loss, laser acupuncture, and other [5]. In diagnostic purposes ones uses laser radiation during registration of photoplethysmogram and oxygenation level Additionally, such approach is used in devices for investigation of combination scattering spectrum (based on the action of radiation on the fluorescent substances) and tracking of their accumulation zones (which can indicate the possible cancer disease) [6], [7].

Stochastic character of physical and physiological model of optical radiation propagation in biological medias (BM) and tissues (BT) is the main factor for precision and certainty of biomedical diagnostic method. The following problems are also significant in the mentioned case:

- the uncertainty of character of scattering spatial indicatrix [8]–[11]. This determines the scattering anisotropy factor and the necessity of its investigation for the specific BT sample with the known geometric parameters;
- the significant weakening of collimated probing radiation. The reasons are substantial difference in the refractive indexes and relatively high BT surface layer scattering coefficients [12], [13];
- the influence of BT layers distribution boundary geometry. This results in the extinction coefficient growth from the one side, and significant spatial redistribution of forward and back scattered light[14], [15];
- balancing during the selection of the wavelength of incident light, applied for increasing of both

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probing depth and resolution during the registering of optical stimulus feedback [16];

- the necessity of consideration of energetic parameters of probing radiation. Such parameters significantly influences the light scattering by thin layers of BT with strong scattering properties [17], [18].

The last two factors can be adjusted by the selection of the corresponding element base and engineering design of the projected device. The first three ones refer to the properties of investigated BM and can be changed by the physical or chemical influence (compression, tension, dehydration, coagulation, refrigeration, introduction of different chemical solutions, gels or oil[19]). In many researches such approach is called “control of optical properties of biological tissues” [20], [21]. One of such control procedures is tissue optical clearing, which performs by adding of special chemical solutions (clearing agents). The purpose of clearing is adjustment of refractive indexes of structural components of BT and surrounding substances scattering; and reduction of scattering coefficient [19].

The mentioned investigation of the specificity of optical clearing implementation performs in the various branches of medicine and technologies, including the conditions of *post mortal* experiments or involving animals. There exists the technology in gynecology for treatment of female urinary incontinence with the means of laser irradiation by the visible and near infrared radiation in the range 500 – 800 nm [22]. For improvement of photons delivery to the necessary depth, there was used BT optical clearing. The experiment was performed on the vaginal tissue samples, which had been taken from the corpses. As the result, the saturation of tissues by glycerin increased the light penetration up to 65%. Other investigations, performed with the goal of the internal cranium components visualization improvement [23], allow to visualize the dendritic spines and microglia of mice brain, and also various neurobiological phenomenon.

All clearing agents were successfully classified in the investigation [24] and divided into multi-atomic alcohols, sugar, organic acids, and other organic solvents. The most widespread agents for human skin clearing are polyethylene glycol [25], glycerin [26], and sugars with the high content of fructose [27].

There exist multiple methods and informational-measuring systems for estimating of BT optical clearing level. Such methods include optical coherence tomography, fluorescent microscopy, multi-photon microscopy, Raman spectroscopy, confocal microscopy, and other.

Optical coherence tomography is based on investigation the ray spectrum as a result of interference, which is further registered by the spectrometer and high-speed CCD cameras. The source for coherent radiation is usually wide-band super-luminescence diode. Parameters for optical clearing level are calculated based on the registered spectrum complex, which was created due to the reflection from the variously dived structures [28], [29].

Double photon microscopy uses the excitation property of fluorophore molecules during the interaction with two photons with less energy (unlike single photon impact), and further registering of fluorescence. This allows to increase the depth of BT optical probing. As the light source, there uses infrared impulse laser with low beam divergence. After reaching to the molecule, the rapid transition of electron on the unstable level occurs (with further returning back). Such transition is accompanied by the quantum irradiation in the green spectrum, which is registered by photo multiplier and further processed [30], [31].

Raman spectroscopy allows to determine the chemical content of BM based on the analysis of inelastic light scattering properties. The most often there uses laser irradiation of visible and near infrared spectrum, the scattered part of which is registered and analyzed as the Stokes or anti-Stokes frequency shift. The modification of method is micro spectrometry, which uses microscope together with spectrophotometer. The image from the microscope is formed as a result of scanning and registration of Raman signal in each point of BT [32], [33].

Confocal microscopy allows to create highly contrast images by BT step-by-step scanning with spatial filtering of backscattered radiation due to the setting of appropriate diaphragms [34], [35].

Additionally to high productivity and precision of described methods and tools, their use requires complex calculation mechanisms and significant computing capabilities. Thus, in many applied tasks for estimating of clearing level there uses standard spectrometers and photometers. Considering the optical clearing goal for tasks of non-invasive diagnostic and therapy of human skin, their application is significantly limited. For investigations in *ex vivo* or *in vivo*, the measuring scheme and construction of device will become much complicated and will require the using of additional devices and tools. The number of applied implementations of photometers with ellipsoidal reflectors [36]–[39] had significant results during the optical properties determination of different biological tissues and medias. Moreover, there were applied rather simple realization scheme and experimental procedure.

Thus, the analytical review showed that the existing typology of measuring tools for optical clearing level control of human skin, has significant functional limitations. At *in vivo* experiment condition, this may lead to reduced reliability of the results of optical biomedical analysis. Considering the mentioned information, the purpose of the current research is the control of the human skin optical clearing level during the evaluation of photometric images illuminance in the mirror ellipsoid of revolution method.

II. METHODS AND TOOLS

The mechanism of optical clearing level control was realized as a model experiment of light propagation in biomedical photometer with ellipsoidal reflector. The construction of the model photometer suggests to proceed the investigation in the reflected (back scattered) light with one ellipsoidal reflector as the base for measuring core of biometric system.

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Fig. 1 represents the structural scheme of biomedical photometer prototype. It was used during the BT optical properties determination at authors research in inverse Monte Carlo method[8], [40] and four-flux Kubelka-Munk model [41].

The operation principle of photometer is based on the directing the collimated radiation from the laser source 1 by means of reflecting prism 2 to the surface of multi-layered biological tissue (in the specific example, such tissue is the human skin). The laser 1 and prism 2 includes the laser beam formation system; and are placed inside the tube 3. Geometrical axis of tube and optical axes of laser and prism coincide the minor semi-axis of ellipsoidal reflector 4. At the same time, the prism 2 is placed in the geometrical center of ellipsoid of revolution (ER) and refracts the incident ray beam by the 90°. In such manner, it coincides the major semi-axis of ellipsoid of revolution. Ellipsoidal reflector is placed orthogonal to the section in its focal plane relatively to its major semi-axis. Due to such phenomena, all back scattered light left the surface of investigated BT and coincides with the ellipsoidal focal plane F1, is gathered by the ER 4 and by ray-tracing mechanisms [38] with further transmission into the second focal plane F2.

The conic optical hood 5 prevents the entering of background radiation in photometer receiving channel, thus improving the biometry precision. The lens 6 makes a projection of the spatial distribution of scattered radiation from the ER second focal plane into the photo-sensitive plane of CCD camera 7. The received photometric image is the precondition for further zone analysis in correspondence to its structure [37].

The photometer operating model interpretation suggests the forming the photometric images of reflector second focal plane as a Monte-Carlo simulation result of light propagation in system “multi-layered biological tissue + ellipsoidal reflector” [36]–[41].At the same time, the light source parameters in simulation are regulated by the software by means of setting the required photons quantity and cross section profile for the laser central mode during its operation in continues wave single-mode regime. Parameters of ellipsoid of revolution corresponds to real photometer reflector and have following values: eccentricity 0.66, focal parameter 16.875 mm, reflection coefficient 0.95.

Initial parameters for modeling are optical properties, which characterizes the dependency of set of parameters from the duration of clearing by polyethylene glycol, received from analytical models and investigation result, represented in researches [19], [22], [42]–[44]. Such parameters set includes scattering μ_s and absorption μ_a coefficients, and scattering anisotropy factor g and refractive index n of human skin separate layers. At the same time, the kinetic of scattering coefficient change for corneous layer, epidermis, and derma is represented on Fig.2.

The constant values of human skin layers optical properties are represented in Table 1.

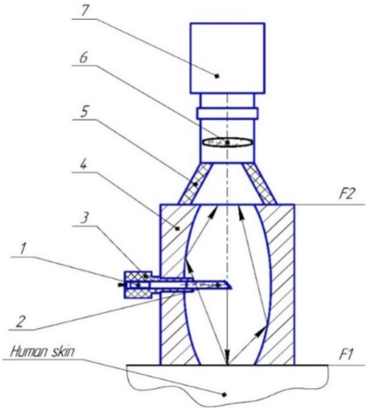

Fig.1 Scheme of photometer with ellipsoidal reflector: 1 – monochromatic light source; 2 – reflecting prism; 3 – tube of formatting system for incident light beams; 4 – ellipsoidal reflector; 5 – conic optical hood; 6 - lens; 7 – CCD camera

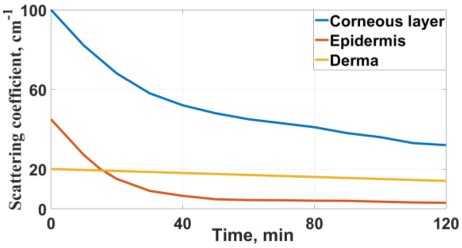

Fig.2 The kinetics of scattering coefficient μ_s (cm^{-1}) of corneous layer (blue line), epidermis (red line) and derma (yellow line) from the clearing time t (min)

TABLE 1 OPTICAL PROPERTIES OF HUMAN SKIN LAYERS

Layer	g	n	μ_a, cm^{-1}	μ_s, cm^{-1}
Corneous layer	0,8	Fig.3	0,10	Fig.2
Epidermis	0,8	1,36	0,15	Fig.2
Derma	0,76	1,39	0,073	Fig.2
Adipose tissue	0,8	1,44	0,068	15
Muscle tissue	0,9	1,37	2	215

This fact doesn’t mean the absence of even minimal polyethylene glycol influence on the human skin properties during clearing (despite of the fact that it wasn’t determined by authors during the analytical search). This fact can be considered as the confirmation of the clinical researches necessity for determination of the numeric values of human skin optical properties in the therapeutic window during the clearing by various agents.

The dependency of the human skin corneous layer refractive index from the optical clearing time is represented on the Fig.3.

The light scattering in both forward and back scattered directions during the photometry by ellipsoidal reflectors can be determined by the thickness of investigated BM sample [36], [37]. Table 2 represents the data of anatomic thickness of human skin layers, which were used during simulation for the different zones of photometric images illuminance estimation. To ensure the “non-invasive” nature of modeled experiment, the value of thickness of muscle tissue layer equals to 1 cm, and ensures conditions of half-infinity of investigated media.

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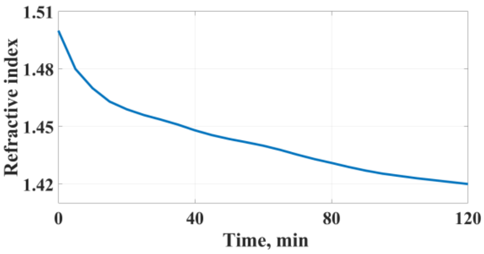

Fig.3 The dependency of corneous layer refractive index from the clearing time t (min)

TABLE 1 ANATOMIC THICKNESSES OF HUMAN SKIN LAYERS [45], CM

Body section	**Corneous layer**	**Epidermis**	**Derma**	**Adipose tissue**
Abdomen	0,0025	0,00945	0,198	1,05
Back	0,0031	0,01	0,371	0,083
Palm (hand)	0,039	0,0473	0,128	0,181
Chest	0,002	0,00595	0,24	0,075
Thigh	0,004	0,011	0,243	0,097
Shoulder	0,0035	0,0107	0,246	0,072

III. RESULTS AND DISCUSSION

During the Monte-Carlo simulation there were emitted 20 million photons. These photons were distributed in the central mode of laser beam with the radius 0.7 mm. During the simulation in multi-layered human skin tissue and ellipsoidal reflector, there were received series of photometric images (size 453x453 pix with a scale of 10 [38]), the examples of which are represented on Fig.4. The modeling was performed for data set, which characterizes the optical properties change considering the 5-minute interval starting from the introduction of polyethylene glycol into the human skin. The maximum observation time was limited by 120 minutes, like in researches [43], [44].

The quantitative evaluation of optical clearing level was performed based on the zone analysis principles of photometric images at ellipsoidal photometry, which appears during axial-symmetry character of scattering [37], [38].

Fig. 5 represents the relation the different illuminance zones of photometric images in backscattered light. Such experiments were performed during the optical clearing with polyethylene glycol for human skin from different body sections. The point on Fig.5, which characterizes the clearing time 0 minutes, is the clearing agent action countdown; but from the physical standpoint it characterizes the human skin optical properties before introducing of polyethylene glycol.

Graphs of illuminance zones of photometric images from different body sections of human skin, depending on the time of optical clearing for middle and external rings [37], have the similar shape. From the one side, this is the proof of the mathematical model adequacy of light propagation in biomedical photometer. From the other side, this allows estimating of the influence of clearing agent action on the light scattering by human skin from different body sections.

The illuminance graph of middle ring of photometric images (Fig. 5, a) express the tendency for rapid growth during the first 20 minutes after introduction of polyethylene glycol. The tendency is valid for the human skin from all investigated body sections. After that, there occurs the moderate decline to the end of the investigation interval in the range 1–3%. The biggest relative growth of illuminance of middle ring is observed for the palm (hand) skin, which can be explained by the biggest corneous layer thickness (comparing to other investigated sections). Considering the scattering coefficient character of corneous layer (Fig. 2), this is the proof of high efficiency of the optical clearing in the first 20 minutes of chemical agent action. The mentioned fact directly correlates with the trend of the refractive index change (Fig.3). The decline of this index in the first 20 minutes of optical clearing is similar to the change during the following 100 minutes.

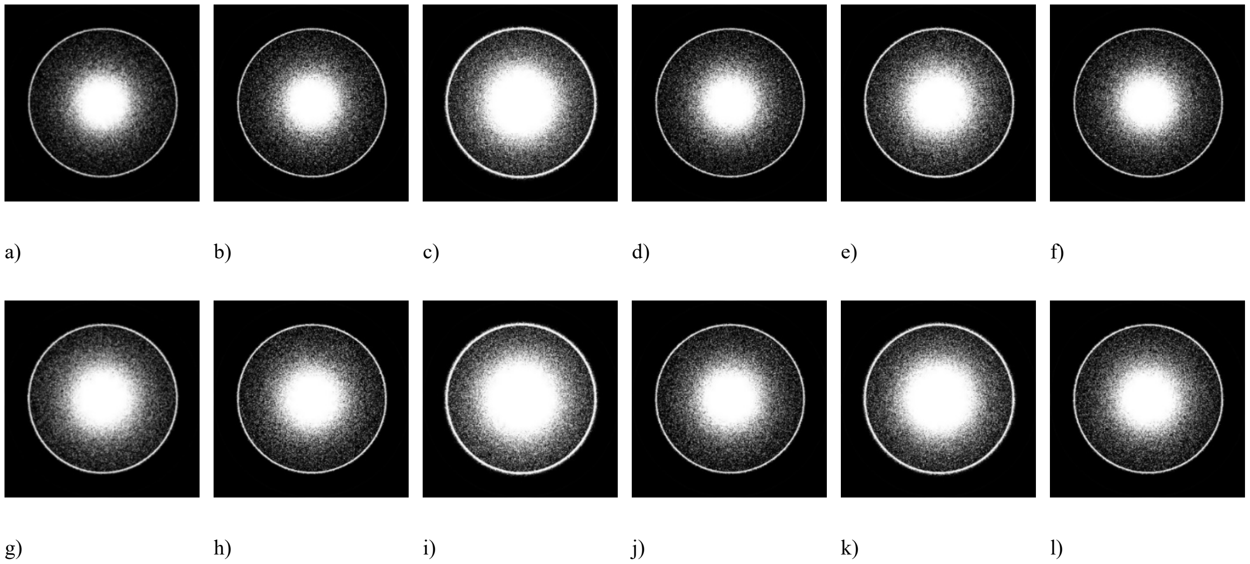
a) b) c) d) e) f)
g) h) i) j) k) l)

Fig.4. Photometric images of back scattered light for human skin tissues before clearing (a, b, c, d, e, f), and on the 70th minute after clearing (g, h, i, j, k, l) during the investigation of skin sections from palm (hand) (a, g), chest (b, h), abdomen (c, i), shoulder (d, j), back (e, k), and thigh (f, l)

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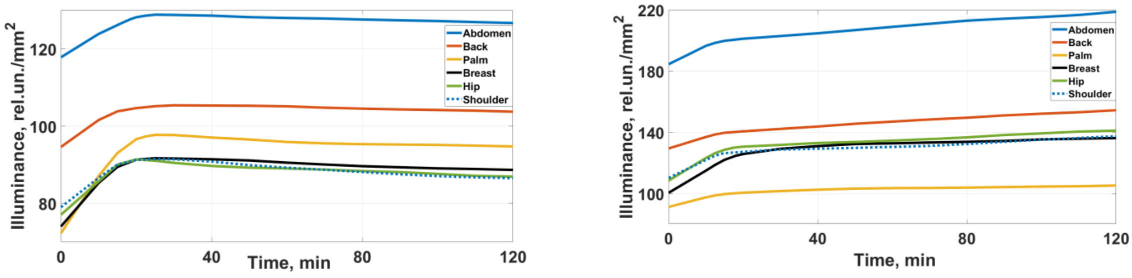

a) b)

Fig.5 The illuminance of the middle (a) and external (b) ring of photometric images depending on the clearing time of human skin from different body sections

The illuminance of external ring depends on the time of optical clearing (Fig. 5, b). It has the similar nature with the illuminance of middle ring in the first 20 minutes of polyethylene glycol action. However, in the following 100 minutes, the illuminance growth continues more moderately, which is caused by the absolute value commensuration with the previous short interval. The lowest dynamic of growth of external ring illuminance on whole interval demonstrate the graph for palm (hand) skin. Considering the dependency, which is represented on Fig.2, such trend means the rapid decline in the scattering coefficients values of corneous layer and epidermis, and also the corneous layer refractive index. Thus, there significantly increases the part of rays, which are located near the collimated reflection area during the observation in the backscattered light. The diffuse constituent of scattered flux is mostly influenced by the illuminance of the external ring, and this value is growing more slowly. The graph of external ring illuminance for back and abdomen skin has also the similar tendency. This can be explained by the bigger derma thickness comparing to other body sections (for back) and adipose tissue (for abdomen), which also can lead to the increase the backscattered light part. Sections of skin from chest, thigh, and shoulder have more rapid rate of growth of external ring illuminance in the first 20 minutes (comparing to the light scattering by other sections of human body). These phenomena can be explained by the absence of factors for slowing of growth of external rings illuminance. These factors are corneous layer thickness – for skin of palm (hand), derma thickness skin for back, and adipose tissue thickness for abdomen.

During the analysis of graphs on the Fig. 5 from the standpoint of illuminance level (i.e. optical clearing level), it can be observed that the highest illuminance for middle and external rings of photometric images is provided by the effects of backscattering by the abdomen skin sections. The middle ring illuminance of abdomen tissue exceeds the same illuminance for human skin from other body sections on more than 25%. For external ring illuminance, such excess is more than 55%. The different zones of illuminance of photometric images for tissues, received from the chest, thigh, and shoulder sections, have similar dependency from clearing time. The phenomena can be explained by the small difference between the anatomic thicknesses of corresponding layers (Table 2). The small difference (up to 10%), which can be observed during the first 15 minutes after introduction of polyethylene glycol into the skin in chest, thigh, and shoulder, is reducing down to 5% during the remaining observation interval. Comparing to the values of anatomic thicknesses of human skin layers on different body sections, and considering the illuminance, which was made in photometric images, the significant advantage of abdomen skin section illuminance can be explained by the significant thickness of adipose tissue. During the constant absolute value of scattering coefficient, equal to 15 cm^{-1}, the increasing of thickness of adipose tissue layer leads to the increase of backscattered light. The relative photons distribution, which had left the BT, depends on the movement trajectory inside the tissue [37], [38]. It is almost uniform in both first focal plane aperture (caused by the absence of interaction between raising ER sides and/or only one-time reflection) and boundary of second focal plane (double reflection during the interaction with the bottom part of ER and/or multiple reflection during the interaction with the upper part of reflector).

The significant anatomic thickness of derma layer for human back skin determines bigger absolute values of illuminance of photometric image zones, comparing to the skin of palm (hand), chest, thigh, and shoulder.

The relative positioning of human skin illuminance graphs on investigated body sections for both middle and external rings of photometric images are similar, except of palm (hand) skin illuminance graphs. The illuminance of external ring has the lowest absolute value. This can be explained by the high efficiency of clearing because of the reduction the corneous layer refractive index under the influence of polyethylene glycol. At the same time, it causes the rapid increase of the quantity of rays in the area of collimated reflection, and, correspondingly, and reducing of the quantity of rays, which forms the diffusive component on the whole observation interval.

In this research there is defined that the optical clearing with the use of polyethylene glycol is performed similar influence on the human skin on various body sections. This leads to the optical properties change of corresponding layers. During the use of optical clearing for delivering of the laser radiation through the human skin, it is necessary to consider the localization of the organ or disease for selection of the appropriate radiation parameters and modes of physical influence. This can be implemented by using of photometers with ellipsoidal reflectors in the pre-diagnosis step prior the chemical agent introduction also. Such approach allows minimizing of

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the possible negative influence of laser radiation in the place of localization and the surrounding tissues. Considering the illuminance distribution for middle and external rings of photometric images (in the first 20-25 minutes after polyethylene glycol introduction), the start of the laser delivery prior to this time pass is unconsiderable. This time is analogical to the "transition period", when the influence of the clearing agent is the less stable and can lead to the undesirable diagnostic artifacts and errors of therapeutic dozing.

CONCLUSIONS

The ellipsoidal reflector method is powerful and promising method for the control of human skin optical clearing level by the different zones of photometric images illuminance level analysis. It ensures the high verification of biological medias types. The illuminance, which is formed in the backscattered light by the human skin on various body sections, is the precondition for selection of effective diagnostic and therapy methods. The ellipsoidal reflector method allows minimizing of possible negative influence of laser radiation in the place of localization and the surrounding tissues. The biomedical photometer with ellipsoidal reflector ensures the optimization of the starting time selection procedure for the laser radiation delivery and its duration according to the fulfilled in the current research modeling prediction of the specific chemical substance agent influence on the human skin clearing.

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Контроль оптичного просвітлення шкіри людини методом еліпсоїдальних рефлекторів

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***Анотація*—Оптичне просвітлення є технологією, що дозволяє шляхом управління оптичними властивостями біологічних середовищ та тканин при введенні в них спеціальних хімічних розчинів, підвищувати діагностичні та**

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терапевтичні показники функціонування різноманітної лазерної апаратури медико-біологічного призначення. Однією з важливих задач лазерних процедур при цьому є контроль рівня оптичного просвітлення, що в багатьох практичних цілях здійснюється з використанням складного та вартісного обладнання. Робота присвячена аналізу особливостей використання методу фотометрії еліпсоїдальними рефлекторами для задач контролю ступеню оптичного просвітлення шкіри людини в умовах неінвазивного експерименту. Модельний експеримент полягає у симуляції методом Монте-Карло поширення оптичного колімованого випромінювання в ядрі інформаційно-вимірювальної системи біомедичного фотометру, що поєднує багатошарову біологічну тканину та еліпсоїдальний рефлектор. Симуляція здійснена для набору оптичних властивостей шарів шкіри людини, зокрема їх коефіцієнтів розсіяння і поглинання, фактору анізотропії розсіяння та показника заломлення, що диференційовано визначаються часом введення просвітлюючого агенту (поліетиленгліколю). Анатомічні товщини рогового шару, епідермісу, дерми, жирової та м'язової тканини умовно визначають ділянку тіла людини, світлорозсіяння шкірою якої досліджувалось. У результаті моделювання отримані фотометричні зображення у розсіяному назад світлі для ділянок долонь, грудей, живота, плеча, спини та стегна. На підставі зонного аналізу отримані залежності освітленості середнього та зовнішнього кільця фотометричних зображень в залежності від часу оптичного просвітлення. Досліджено вплив часу оптичного просвітлення на характер світлорозсіяння шкірою людини різних ділянках тіла Аналіз фотометричних зображень показав, що оптичне просвітлення з використанням поліетиленгліколю, яке призводить до зміни оптичних властивостей відповідних шарів, здійснює подібний влив на шкіру людини на різних ділянках тіла. При використанні оптичного просвітлення з метою доставки лазерного випромінювання через шкіру людини необхідно врахувати локалізацію органу або захворювання для підбору відповідних параметрів випромінювання та режимів фізичного впливу. З огляду на розподіл освітленості середнього та зовнішнього кільця фотометричних зображень у перші 20-25 хвилин після введення поліетиленгліколю, раніше розпочинати процедуру доставки лазерного випромінювання недоцільно. Цей час є аналогом «перехідного процесу», коли вплив просвітлюючого агенту є найменш стабільним і може призвести до небажаних діагностичних артефактів та похибок терапевтичного дозування.

Бібл. 45, рис. 5, табл. 2.

Ключові слова — оптичне просвітлення; еліпсоїдальний рефлектор; шкіра людини; фотометричне зображення.

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Контроль оптического просветления кожи человека методом эллипсоидальных рефлекторов

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***Аннотация*—Работа посвящена анализу особенностей использования метода фотометрии эллипсоидальными рефлекторами для задач контроля степени оптического просветления кожи человека в условиях неинвазивного эксперимента. Модельный эксперимент состоит в симуляции Монте-Карло распространения оптического излучения в многослойной биологической ткани и эллипсоидальном рефлекторе. Для набора оптических свойств слоев кожи человека и их анатомических толщин полученные фотометрические изображения в рассеянном назад свете для участков ладони, груди, живота, плеча, спины и бедра. На основе зонного анализа получены зависимости освещенности среднего и внешнего колец фотометрических изображений от времени оптического просветления. Исследовано влияние времени оптического просветления на характер светорассеяния кожей человека разных участках тела.**

Библ. 45, рис. 5, табл. 2.

Ключевые слова — оптическое просветление; эллипсоидальный рефлектор; кожа человека; фотометрическое изображение.