UDC 51.76, 519.6

Human Cornea Modeling using Artificial Collagen

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This article focuses on spectrophotometric analysis of thin films of synthetic collagen with subsequent use of the received data to recover the optical properties of collagen and modeling a multilayer optical structure similar to the properties of human cornea.

Key words and phrases: collagen, thin collagen films, human cornea, keratoprosthesis.

1. Introduction

Cornea is optically transparent part of the outer shell of the eyeball, which performs approximately three-quarters of the work on refraction and focusing a beam of light on the retina. Various damages caused by mechanical, chemical or microbiological effects, with high probability lead to total or partial loss of vision. Small erosions occurring on the surface of the cornea, close in several days, but in case of damaging of deeper layers, the site of the defect appears translucent haze, which can lead to a significant reduction in vision, especially if the injury occurred in the central zone of the cornea. At least 10 million people all over the world are blind because of the damaged or diseased corneas.

Till recently keratoplastics was the only way to help these people. This is a surgical procedure where a damaged cornea is replaced by donated corneal tissue. The main problem of this approach is deficiency of donor tissue. Each year over 100000 people are waiting for cornea transplants. More universal method which allows obviating necessity for donors is keratoprosthesis. The most widely used keratoprosthesis such as AlphaCor (Lions Eye Institute, Argus Biomedical Pty Ltd), Boston K-Pro, have standard design: all models include plastic optical part and differ from each other by fasting to the cornea. The main problems of these keratoprosthesis are high percent of rejection of an artificial cornea, its keratomalacia and opacity.

Collagen is one of the most promising biomaterials in medical practice, it has a wide range of applications. It is a native material for the human cornea, and therefore one of the most important applications of collagen is its use to develop an artificial cornea, so-called keratoprosthesis and it is necessary to know the optical properties of thin films of collagen, such as the dependence of reflection and transmission coefficients from medium acidity, properties of light scattering on collagen structures, etc. Spectrophotometric research and multiple solving of inverse problem allow determining these parameters. The obtained data is used in the mathematical synthesis of collagen structures with predetermined characteristics such as artificial cornea. Merits of collagen keratoprosthesis: almost absolute biological compatibility; reducing terms of the operations performing and postoperative rehabilitation to a minimum; reproducing biomechanical characteristics of natural cornea; wider patient base.

2. Spectrophotometric Research of Collagen

Specialists of Fibralign Corporation, CA, USA developed the technology of synthesis of collagen type II and the formation of structures with predetermined characteristics, including thin films, which can be used in the problem of creating an artificial cornea of the human eye. For the use of artificially produced collagen films in solving

Received 10^{th} May, 2011.
This work was supported by research topic PFUR №020617-1-174.

this problem they need to be comprehensive researched, including — spectrophotometric.

Research of available samples were made using “Optics Research Laboratory” equipment, including spectrophotometer Lambda-950, manufactured by PerkinElmer, USA, and profilometer DekTak 150, manufactured by Veeco Instruments Inc, USA.

As materials for the research were used samples of different thickness and samples consisting of different number of layers: one, two, four and six, as well as samples with different types of fastening: on the glass substrate and the special cassettes. Optical properties of artificial collagen were priori unknown.

Measurements of reflection and transmission coefficients were conducted with the help of spectrophotometer Lambda 950. We used the visible spectrum — from 400 to 800 nm as the range of wavelengths. In order to determine optical properties of collagen, the measurements were performed for single layer sample, fixed in the cassette. This approach has several advantages: it is easier to use the results for solving the inverse problem of recovering, and substance by which layers in multilayer samples are fastened may introduce error into the results of spectrophotometric measurements.

The thickness of the collagen film on the substrate was also measured using profilometer DekTak150. Collagen layer covered the substrate not fully, so it was possible to measure the difference in height of the sample and the substrate, which is the film thickness.

3. Restoration of Collagen Optical Properties

To solve the problem of mathematical synthesis of collagen keratoprothesis it is necessary to determine the optical properties of synthetic collagen. The problem of restoration of the dielectric tensor and thickness of thin anisotropic films using measurements of reflected and refracted waves is formulated as follows. Using sets of spectrophotometric data about transmission $\tilde{T}(\lambda)$ and reflection $\tilde{R}(\lambda)$ it is necessary to calculate the parameters of the dielectric tensor of the material $\hat{\varepsilon}(\lambda)$ in the range of wavelengths $[\lambda_{\text{start}}; \lambda_{\text{end}}]$. This is the mathematically ill-posed problem.

Using sets of measured energy coefficients of reflection and transmission and methods of numerical optimization we can recover the dielectric tensor and thickness for each wavelength separately and obtain the indexes of refraction and absorption, which together constitute the complex refractive index: $\tilde{n} = n+ik$. Complex refractive index and dielectric tensor linked as following: $\tilde{n}(\omega) = \sqrt{\hat{\varepsilon}(\omega)}$. However, practice shows that the results of these calculations are unstable — the dielectric tensor is restored in the form of a non-smooth function. Therefore, there is a need to use any method of solving problems for all investigated range of wavelengths, typically an optical range — 400–800 nm. Reconstruction algorithm in this case is much more complicated, but allows using of a priori information about the decision and apply the methods of regularization. As an a priori information there were used the dispersion of the Kramers–Kronig — integral relation between the real and imaginary parts of analytic complex functions [1].

The propagation of polarized light in multilayer anisotropic structure can be described by a matrix equation for the vector of tangential components of reflected and transmitted fields χ_R and χ_T with initial conditions – information about tangential components of incident field χ_I [2, 3].

The proposed algorithm for solving the inverse problem lies in the approximation of the imaginary part of dielectric tensor — sum of Gaussian functions (or, otherwise, the approximation by radial basis functions) and using the Kramers–Kronig relations to calculate the real part of this function. The objective function, that expresses the sum of squared differences between measured and calculated energy coefficients of reflection and transmission, is minimized by the Nelder–Mead algorithm.

The described algorithm is implemented in software “MorphoVision”, developed in the lab “Optics of nanostructures” in People’s Friendship University. The initial parameters of the software takes the data sets, each set must contain a sample thickness, the angle of incidence on the sample, the polarization of light (TE or TM), text files with energy coefficients of reflection and transmission.

The calculation procedure using the proposed algorithm is different for different types of materials (isotropic material, a uniaxial anisotropic material, biaxial anisotropic material). In the case of uniaxial anisotropic material, which is the collagen (as identified by polarizing scanning) is sufficient to hold two-cycle recovery. To obtain the refractive and absorption indexes along one direction it is necessary to use data on the energy reflection and transmission coefficients obtained from the measurements when the plane of light incidence was parallel to the optical axis. To obtain the refractive and absorption indexes along the other direction we should use spectrophotometric data obtained when the plane of light incidence on the sample was perpendicular to the optical axis. We carried out a series of calculations and obtained the coefficients of refraction and absorption of artificial collagen.

4. Synthesis Algorithm

After the refractive indices of synthetic collagen were recovered, we can solve the problem of synthesis of multilayer optical structure of collagen, which has geometric and optical characteristics similar to the characteristics of human cornea. Problem of mathematical synthesis of optical systems with specified characteristics are a large class of inverse mathematical problems, and they are usually ill-posed. There are different approaches to solve them, but the most effective of these is the method of Tikhonov regularization [4].

As initial data we have recovered optical properties of collagen, maximum and minimum thickness of the simulated system (the thickness of a human cornea is about 0.5–0.7 mm), maximum and minimum thickness of one layer, the desired spectral characteristics of reflection and transmission of the simulated system (the transmission not less than 60% in the optical range, which corresponds to transmission of adult human cornea). Our task is to determine the number of layers of the system, the angles at which they are located relative to each other and the thickness of the layers of the system.

Let $\widehat{T}(\lambda)$ — defined on the wavelength range $[\lambda_1, \lambda_2]$ — be energy coefficient of transmission. We assume $\widehat{T}(\lambda)$ is a general function on $L_2\,[\lambda_1, \lambda_2]$. The direct problem of modeling of propagation of light in multilayer optical system can be expressed as:

$$M(h, \hat{\varepsilon}, \theta_j)\vec{A} = \vec{D};\ \vec{A} \Rightarrow \vec{R}, \vec{T}. \tag{1}$$

Vector $\vec{D}$ includes amplitudes of reflected and transmitted waves. Energy coefficients of transmission and reflection can be calculated using these amplitudes. Required properties of simulated optical system expressed as: $M(d^0, \hat{\varepsilon}, \theta^0)\vec{A}^0 = \vec{D}$; $\vec{A}^0 \Rightarrow \vec{R}^0, \vec{T}^0$.

Thus, to solve the problem it is necessary to minimize the functional:

$$F(\vec{T} - \vec{T}^0, \vec{R} - \vec{R}^0) \to \min, \tag{2}$$

where $\bar{T}_0$ and $\bar{R}_0$ are required transmission and reflection of simulated optical system, and $\bar{T}$ and $\bar{R}$ — calculated transmission and reflection. Problem is solved by Tikhonov regularization. Let $\delta_N = \inf \left\| A(x, \lambda) - A^0(\lambda) \right\|_{L_2}$ be the maximum achievable accuracy of approximation on optical system consists of N layers. Maximum achievable accuracy satisfy the estimates $\delta_1 \geqslant \delta_2 \geqslant \ldots \geqslant \delta_N \geqslant \ldots \geqslant 0$ and together they are bounded below by $\delta = \lim\limits_{N\to\infty} \delta_N$, which we call the maximum possible accuracy.

It is necessary to minimize the residual (2), approximating the desired response with a given accuracy. Introduce an error: $S(n, N)$, where n — number of layers in the system, and N — the number of iterations in the computation. If the selected number of layers at step N is achieved the specified accuracy, the algorithm stops, the result has been obtained. If $S(n)$ is more than a specified accuracy, then move on to the system of $(n + 1)$ layers, then — to a system of $(n + 2)$ layers, and so on. If the number of layers exceeds the maximum (or the thickness of the system exceeds the maximum), then should be pointed out the impossibility of achieving the required characteristics to these terms.

5. Conclusions

Using created software we have performed series of calculations and synthesized a variety of structures with desired characteristics. To select the optimal structure, which could be used as a keratoprosthesis, further joint work of many professionals is needed — from engineers involved in the production of stacks of synthetic collagen and ending with scientists in the field of eye medicine.

References

1. *Ландау Л. Д., Лифшиц Е. М.* Электродинамика сплошных сред. — 4-е издание. — М.: Физматлит, 2005. [*Landau L. D., Lifshic E. M.* Ehlektrodinamika sploshnihkh sred. — 4-e издание. — M.: Fizmatlit, 2005.]
2. *Ловецкий К. П., Хохлов А. А.* Моделирование взаимодействия электромагнитной волны оптического диапазона с анизотропным слоем // Вестник РУДН, серия «Математика. Информатика. Физика». — 2010. — Т. 1. — С. 93–100. [*Loveckiyj K. P., Khokhlov A. A.* Modelirovanie vzaimodeyjstviya ehlektromagnitnoyj volnih opticheskogo diapazona s anizotropnihm sloem // Vestnik RUDN, seriya «Matematika. Informatika. Fizika». — 2010. — T. 1. — S. 93–100.]
3. *Хохлов А. А.* Решение задачи описания прохождения электромагнитной волны через слоистую среду // Вестник РУДН, серия «Математика. Информатика. Физика». — 2010. — Т. 2. — С. 103–105. [*Khokhlov A. A.* Reshenie zadachi opisaniya prokhozhdeniya ehlektromagnitnoyj volnih cherez sloistuyu sredu // Vestnik RUDN, seriya «Matematika. Informatika. Fizika». — 2010. — T. 2. — S. 103–105.]
4. *Гласко В. Б., Тихонов А. Н., Тихонравов А. В.* О синтезе многослойных покрытий // Журнал вычислительной математики и математичекой физики. — 1974. — Т. 14, № 1. — С. 135–144. [*Glasko V. B., Tikhonov A. N., Tikhonravov A. V.* O sinteze mnogosloyjnihkh pokrihtiyj // Zhurnal vihchisliteljnoyj matematiki i matematichekoyj fiziki. — 1974. — T. 14, No 1. — S. 135–144.]

УДК 51.76, 519.6

Моделирование роговицы человеческого глаза с применением искусственного коллагена

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Статья посвящена спектрофотометрическому анализу тонких пленок из искусственного коллагена с последующим применением полученных данных для восстановления оптических свойств коллагена и моделированию многослойной оптической структуры, аналогичной по свойствам роговице человека.

Ключевые слова: коллаген, тонкие коллагеновые пленки, роговица человеческого глаза, кератопротез.