Monte Carlo modelling of normal skin and skin cancer Raman spectra

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Abstract. In this paper, we propose an algorithm of Monte Carlo modelling of Raman scattering. A model of Raman scattering in multi-layered tissues has been built. A number and optical properties of tissue layers, number of photons, geometric size of the model and parameters of the light source may be varied by users. Some of computational results have been compared with other investigators.

1. Introduction
Today optical methods such as fluorescence analysis, backscattering spectroscopy and Raman spectroscopy have been increasingly used for the diagnosis of malignant tumours [1, 2]. Raman spectroscopy makes it possible to obtain information about the local structure of skin tumours from spectra of the substances that make up biological tissue [3, 4]. Since these spectra represent a set of narrow peaks, Raman spectra of various biological tissues are specific and can be used to successfully differentiate various pathologies in biological tissues [5, 6]. Recent technical advances in Raman spectrometer hardware have paved the way for exploiting the Raman effects in clinical applications [7, 8]. Due to the ability to do in vivo tests and non-invasiveness Raman spectroscopy has shown great potential in non-invasive cancer screening [9]. It is essential to have an accurate model for illustrating the properties of Raman excitation and Raman photon escape process in order to facilitate the quantitative analysis of in vivo Raman spectra.

2. Skin model
In this paper the human skin is investigated. According to [10], human skin is a complex heterogeneous structure – a multicomponent turbid biological environment. In this study the model shown in figure 1 [2] is used. From the point of view of the implementation of the program algorithm it is necessary to have a discrete model of biological tissue. The medium is defined as a cube with cube-shaped voxels. Each voxel is assigned an integer value which identifies a particular type of tissue with unique optical properties of an absorption coefficient, scattering coefficient, anisotropy factor, and refractive index.

The skin model consists of two layers: the epidermis and the dermis. The size of the model is 3x3x5 mm, that is, 300x300x500 voxels. The epidermis layer is 0.2 mm, and the dermis layer is 4.8 mm. The number of the layers, their thickness, shape and other characteristics can also be changed by the user.
In this study the approach described in [10] is used to determine optical transport parameters of a skin model. In addition to the “background” optical transport parameters, each voxel is characterized by the concentration of Raman active skin components, which form heterogeneities in tissue caused by pathological processes. As the most important model components collagen, elastin, keratin, cell nucleus, triolein, ceramide, melanin and water are chosen (table 1). The basis spectra of those skin constituents have been used to simulate human skin spectra. We used the spectra and key biophysical changes of skin components with different tissue types by Xu Feng et al. [13] The light source is modeled as a collimated beam with a frequency of 785 nm, located in the middle of the plane $z = 0$. The direction of light is perpendicular to the tissue.

### Table 1. Skin components in percentage for different tissue types (the arrow indicates the most characteristic changes for each lesion type).

|                | Normal skin | Malignant Melanoma | Basal Cell Carcinoma |
|----------------|-------------|---------------------|----------------------|
| Collagen       | 18%         | 18%                 | 15%↓                 |
| Elastin        | 12%         | 14%                 | 23%↑                 |
| Triolein       | 41%         | 11%↓                | 28%↓                 |
| Nucleus        | 9%          | 6%                  | 20%↑                 |
| Keratin        | 1%          | 2%                  | 1%                   |
| Ceramide       | 9%          | 17%↑                | 4%                   |
| Melanin        | 5%          | 29%↑                | 3%                   |
| Water          | 5%          | 3%                  | 6%                   |

3. Methodology

3.1. Raman scattering

Raman scattering is the inelastic scattering of a photon by molecules. The scattered photons have a frequency and energy different from those of the incident photons. The difference in energy for each inelastically scattered photon corresponds to a molecular vibration of a particular component of the specimen. Raman light scattering was discovered in 1928 simultaneously by Soviet physicists G.S. Landsberg and L.I. Mandelstam during the study of light scattering in crystals and by Indian physicists C.V. Raman and C.S. Krishnan during the study of light scattering in liquids [12, 13]. Raman spectroscopy is an effective method for studying the structure of molecules and the processes of their interaction with the environment. The molecular vibrations of each substance produce a characteristic Raman fingerprint spectrum that can be used to determine the chemical and structural composition of the sample.

Recently, Raman spectroscopy as a non-destructive method of laser diagnostics starts to be used in medical research. A comparative analysis of the Raman spectra of malignant and benign skin neoplasms allows us to determine specific types of skin tissue [14]. The classical objects for interpreting of the biomolecules Raman spectra are proteins and their components. Analyzing the
position of the maximum and the shape of the spectrum it is possible to obtain quantitative estimates
of the content of some types of structure in the protein. During the process of development of a
pathological neoplasm, a change in the biochemical composition of biological tissue occurs, which
leads to a change in the Raman spectra measured in vivo, depending on the geometric characteristics
and composition of the tissue [9].

3.2. Monte Carlo method

The Monte Carlo method refers to a group of numerical methods for solving mathematical problems
by simulating random variables. From the point of view of solving the radiation transfer equation, the
Monte-Carlo method is computer simulation of random trajectories of the number of photons (N) [15,
16]. To obtain an acceptable approximation, it is necessary to consider a large number of photons,
since the accuracy of the results is proportional to N.

The main idea of the method is to take into account the phenomena of absorption and scattering
throughout the photon optical path through a turbid medium. The distance between two collisions is
selected from the logarithmic distribution using a random variable. To account absorption, each
 photon is assigned a weight, and this weight is constantly reduced when the photon propagates through
the medium. If scattering occurs, a new direction of propagation is selected according to the phase
function and another random variable. This procedure continues until the photon leaves the medium or
its weight reaches a certain small value. Figure 3 shows the trajectory of a single photon calculated
using the Monte Carlo method. In this case, the photon has completed its path, escaping the medium
(indicated by “*”).

In this study a two-step model of Raman scattering in multi-layered tissues has been built. The
algorithm for simulating Raman light scattering by multilayer biological tissue consists of the main
program (figure 4) and the photon transport subroutine proposed by L. Wang and S. L. Jacques [17].

In the first step, the program simulates the propagation of the incident photons through the sample.
Using a subroutine by L. Wang and S. L. Jacques, photons are excited at the source radiation
frequency, which results in a distribution of the excitation photons within the sample.

In the second step, Raman scattered photons are launched from each point where parent photons
were absorbed in isotropically distributed directions and with a weight of:

$$W_R(x, y, z, \lambda) = F_{ex}(x, y, z) \times \mu_R(\lambda) \times (s_{R1}(\lambda) \times C_1(x, y, z) + \ldots + s_{RN}(\lambda) \times C_N(x, y, z)), \quad (1)$$

where $F_{ex}(x, y, z)$ represents results in a distribution of the excitation photons, $\mu_R(\lambda)$ is comparable
with the Raman probability and depends on the frequency of the emission photons, $s_{R1}(\lambda) \ldots s_{RN}(\lambda)$
are given by Raman spectra of skin components, $C_1(x, y, z) \ldots C_N(x, y, z)$ are concentrations of
components 1 ... N.

In equation (1), the value of $\mu_R(\lambda)$ is determined by the equation:

$$\mu_R(\lambda) = 1/\lambda^4. \quad (2)$$
4. Results & Discussion

In this study, we established a Raman “biophysical model”, a program for modelling Raman spectra. Monte Carlo simulation was performed to record Raman spectra of skin for 785 nm excitation light and for different emission wavelengths at an interval of 10 1/cm from 800 to 1800 1/cm. In each simulation, 1,000,000 photons were launched at the first stage and 1,000 photons for each voxel at the second stage.

4.1. Monte Carlo simulation of normal skin, Malignant Melanoma, and Basal Cell Carcinoma Raman spectra

We obtained Raman spectra spanning normal skin, Malignant Melanoma (MM), and Basal Cell Carcinoma (BCC). We use eight of the most relevant skin constitutes contributing to the spectral differences among different skin malignancies.

Figure 5, (a), (b), (d) shows mean Raman *in vivo* spectra and reconstructed Raman spectra. The Raman spectra were normalized to their respective area under curve. In general, the reconstructed Raman spectra match reasonably well with the *in vivo* Raman spectra. In particular, the major Raman peaks of normal skin Raman spectra reconstructed by this Monte Carlo simulation (1075, 1275, 1450, 1660 1/cm) match very well with the *in vivo* spectra. However, it is possible to observe differences in intensity in the ranges 900-950, 1000-1075, 1125-1225, 1275-1400, 1500-1650 1/cm. This can be
explained by the fact that a limited number of skin Raman active components are used in modelling (table 1), while the in vivo spectrum is the result of the superposition of hundreds of spectra of different substances. In other words, differences in the indicated spectral ranges arise due to the simplicity of the optical model.

![Normalized Raman spectra of normal skin tissue, Malignant Melanoma (MM), and Basal Cell Carcinoma (BCC).](image)

**Figure 5.** Normalized Raman spectra of normal skin tissue, Malignant Melanoma (MM), and Basal Cell Carcinoma (BCC).

There are also differences between the reconstructed and the in vivo Raman spectra in the case of MM and BCC. These differences may be due to the fact that the composition of diseased skin varies depending on the stage of the disease and individual characteristics of patients.

To achieve greater convergence between the experimental and reconstructed Raman spectra, the concentrations of the skin components were changed. The newly accepted concentrations are presented in the third column of table 2.

The reconstructed Raman spectrum is presented in figure 5, (c). The adjustment of concentration values led to a greater similarity between the experimental and reconstructed Raman spectra than in the first case. So, it was possible to achieve proximity of the spectral values in the range of 1550-1650 1/cm and reduce the differences in the intensity of the spectra in the range of 1325-1400 1/cm.

**Table 2.** Normal skin components in percentage.

| Component | Normal skin by Feng X. et al. | Normal skin (corrected concentrations) |
|-----------|-------------------------------|----------------------------------------|
| Collagen  | 18%                           | 13%                                    |
| Elastin   | 12%                           | 7%                                     |
| Triolein  | 41%                           | 41%                                    |
| Nucleus   | 9%                            | 16%                                    |
| Keratin   | 1%                            | 7%                                     |
| Ceramide  | 9%                            | 9%                                     |
| Melanin   | 5%                            | 15%                                    |
| Water     | 5%                            | 1%                                     |
4.2. Determination of changes in the concentrations of skin components during the development of BCC

The skin Raman spectra of several patients, registered in vivo using the laboratory spectroscopic system described in [19], were selected for study. For each patient, the normal skin Raman spectra and the BCC Raman spectra are known. The averaged experimental Raman spectrum of normal skin, obtained by averaging normal skin in vivo spectra of all the patients, is selected as the “background” spectrum. By varying the concentrations of collagen, elastin, keratin, cell nucleus, triolein, ceramide, melanin and water, it is proposed to obtain a spectrum that is closest to the average experimental BCC Raman spectrum. Figure 6 shows the results of simulating the BCC Raman spectrum. The parameters at which the obtained spectrum is closest to the average experimental BCC Raman spectrum are presented in Table 3.

Comparing the reconstructed Raman spectrum with the averaged experimental BCC Raman spectrum, it can be noted that these spectra are fairly well correlated with each other, especially in the range from 1316 to 1723 cm⁻¹. In the range from 1723 to 1799 cm⁻¹, the resulting Raman spectrum is more similar to the normal skin Raman spectrum, and not to the BCC Raman spectrum. Paying attention to the Raman spectra of skin components (figure 6), it can be noted that in the specified range the spectra of the components have not characteristic peaks. This means that during the development of BCC, changes in the composition of the skin are not limited to the components studied, the change in the experimental spectra in the specified range is due to other components.

Figure 6. Raman spectra of normal skin, BCC and some skin components.
Table 3. Changes in the concentrations of skin components during the transition from the normal skin Raman spectrum to the BCC Raman spectrum.

| Change in the concentration of the component (by Feng X. et al.) | Change in the concentration of the component (in this study) |
|---------------------------------------------------------------|--------------------------------------------------------------|
| Collagen                                                      | -3%                                                         | -1%                                                         |
| Elastin                                                       | +11%                                                        | -6%                                                         |
| Triolein                                                      | -13%                                                        | -10%                                                        |
| Nucleus                                                       | +11%                                                        | 0%                                                          |
| Keratin                                                       | 0%                                                          | +4%                                                         |
| Ceramide                                                      | -5%                                                         | -7%                                                         |
| Melanin                                                       | -2%                                                         | -2%                                                         |
| Water                                                         | +1%                                                         | +1%                                                         |

Analysing changes in the concentrations of the skin components, one can identify the following. In the transition from the average Raman spectrum of normal skin to the average Raman spectrum of the BCC, the concentrations of collagen, triolein, ceramide, and melanin decrease, and the concentration of water increases, as also reported in [11]. In the case of elastin, keratin and nucleus, there is a difference in the concentrations from those given in [11]. Thus, in accordance with [11], the concentrations of elastin and nucleus increase by 11%, and the concentration of keratin does not change (Table 3). However, as a result of modelling, the concentration of elastin decreases, the concentration of nucleus does not change, and the concentration of keratin increases. These results may be due to the fact that the composition of BCC varies depending on individual characteristics of patients.

In summary, spectra modelled were found to be consistent in general with previous studies. The algorithm can be used not only to simulate the Raman spectra but also to study the real Raman spectra of patients and determine certain parameters of these spectra. Monte Carlo simulations of photon propagation offer a flexible yet rigorous approach toward Raman scattering in turbid tissues.

5. References
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