Mathematical Model for Analyzing the Fluorescence Emission of Biological Tissue

Modelo matemático para el análisis de la emisión de fluorescencia del tejido biológico

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DOI: https://doi.org/10.22517/23447214.25682
Scientific and technological research paper

***Abstract*—Optical emission fluorescence spectroscopy allows for determining biochemical changes in healthy and pathological biological tissue, either in vivo or in biopsies. The aim of the study is to analyze the chemical and physical properties of cervical tissue. A mathematical model is presented to examine and observe the fluorescence emission of tissue. During the development of precancerous states, the optical properties of the tissue can be altered not only by the light dispersion and the fluorescence increase in the epithelium but for the fluorescence reduction in the stroma. The Beer-Lambert Law was used to describe light propagation in the tissues. Four components of cervix tissue were identified: collagen, elastin, NADH, and flavins. By applying the developed model, it was possible to characterize each fluorophore present through Gaussian sub-spectra, providing support for the medical diagnosis of precancerous lesions in cervical tissue. The model yielded predictions with a good spectral fit, and the contribution of each fluorophore showing significant differences in the signal parameters, particularly for collagen and NADH.**

***Index Terms*—Detection cancer, Fluorophore, Mathematical Model, Optical Fluorescence Spectroscopy, Precancerous Tissue.**

***Resumen*—La espectroscopía de fluorescencia por emisión óptica permite determinar cambios bioquímicos en tejidos biológicos normales y patológicos, ya sea in vivo o en biopsias. El objetivo de este estudio es analizar las propiedades químicas y físicas del tejido cervical. Se presenta un modelo matemático para examinar y observar la emisión de fluorescencia del tejido. Durante el desarrollo de estados precancerosos, las propiedades ópticas del tejido pueden alterarse no solo por la dispersión de la luz y el aumento de fluorescencia en el epitelio, sino también por la disminución de fluorescencia en el estroma. Para describir la propagación de la luz en los tejidos se utilizó la Ley de Beer-Lambert. Se identificaron cuatro componentes en el tejido cervical: colágeno, elastina, NADH y flavinas. Al aplicar el modelo desarrollado, fue posible caracterizar cada fluoróforo presente mediante subespectros gaussianos, brindando soporte al diagnóstico médico de lesiones precancerosas en el tejido cervical. El modelo arrojó predicciones con un buen ajuste espectral, evidenciando diferencias significativas en los parámetros de señal de cada fluoróforo, especialmente en el caso del colágeno y el NADH.**

***Índice de términos*— Detección de cáncer, Espectroscopia óptica de fluorescencia, fluoróforos, modelo matemático, Tejido precanceroso.**

I. INTRODUCTION

CERVIX cancer is the 4th most common cancer in women around the world. Its development is very slow, and it tends to begin with a lesion called cervical intra-epithelial neoplasia (CIN), from which several years can go until it becomes cancer. However, this kind of lesion can be identified in an early stage, and that way, strong actions can be taken to face the illness on time [1]. Early detection of CIN represents a fundamental especially role in the mortality reduction related to cervix cancer, especially during the last 50 years [2]. Opposite of it, nowadays, cervix cancer keeps being a relevant threat to woman's health [1], [2].

For cervix detection, different diagnosis methods have been used such as cytology, HVP molecular detection, and colposcopy [3]. However, the techniques mentioned above are not efficient enough to detect cervix cancer in its early stages, and many times, a histopathological analysis of biopsies is required for the final diagnosis. For example, a sensibility rate of 32 to 90% and 94% of specificity is associated with cytology analysis according to [4], [5] due to the limited number of tests and reading errors. Other diagnosis methods present lower percentages of sensibility and specificity. To improve the variables mentioned above, it is necessary to find other diagnosis methods [5].

An important technique that was used during previous decades to detect cervix pre-cancerous lesions was fluorescence spectroscopy. This technique can offer high sensitivity as well as a specific and accurate diagnosis without extracting the tissue [6], [7]. Even, when there is huge empirical evidence that sensitivity suggests that the mentioned technique can be used to discriminate between normal and dysplastic cervical tissue, there is no wide information to understand the differences in the biological tissue of fluoresce spectrum of normal and dysplastic tissue [8]. The work can be done by developing algorithms to simulate the spectrum.

Fecha de Recepción: 26/01/2024
Fecha de Aceptación:

The aim of this research is to simulate the normal and pathological fluorescence spectrum of cervix tissue by using mathematical models based on the Beer-Lambert law, to study the fluorescence emission of molecules in the tissue such as collagen, elastin, NADH, and flavins. Results are compared with the ones obtained for in-vivo tissue.

II. METHODOLOGY

The following methodology was conducted to conduct the research.

a. Equipment and materials

The system used for the research was composed of an optical fiber probe, a spectrograph, and a computer interface. This equipment was used to record fluorescence spectral data of cervix in-vivo tissue.

Characteristics of laser are:

- Wavelength: 337.1 nm
- Pulse: 5 ns
- Repetition rate: 33 Hz
- Pulsed transmitted energy: 300 µJ

b. Objective Sample

For this research, a pilot test for normal and pathological cervix tissue of 50 patients between 17 and 60 years old was conducted. Patients had previous results of cervical cytology. Informed consent was obtained for each patient and the study was reviewed and approved by specialists of the *IPS-Universidad de Caldas – Unidad de Cáncer de Cuello Uterino y Cáncer de Mama*.

Fluorescence spectra were taken according to the pre-established protocol conducted by experts. Figure 1 shows the cervix and the four points where measurements were done. On each point, 30 spectra were taken, and then, during signal processing, an average spectrum was obtained.

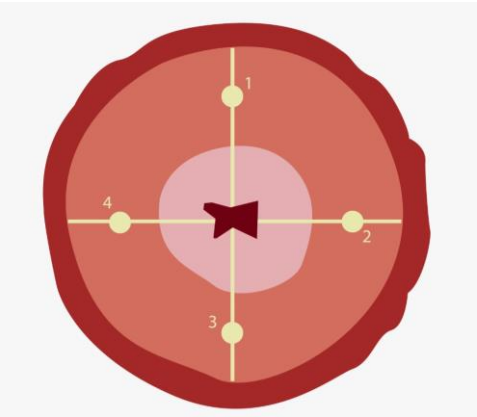


Fig. 1. Sections and points of the cervix to take the spectrum.

III. THEORETICAL FRAME

a. Optical Spectroscopy Fluorescence

Spectroscopy comes from electromagnetic interaction with matter. That produces state transitions for molecules and level transitions for atoms. Transitions can be electronic in the visible spectrum (UV), vibrational in the infrared (IR) or rotational in the radio waves. Spectroscopy relates three processes that are going to be explained in more detail in the following sections: radiation absorption, light emission, and dispersion.

Fluorescence is the ability of certain molecules to absorb energy and emit electromagnetic radiation with different wavelengths. That is why, optical fluorescence spectroscopy is a method to analyze the fluorescence of a sample using a beam of light that can be normally found in the ultraviolet spectral range. Fluorescence is widely used in analytic measurements, and photochemical analysis of biological systems, alimentary products, pharmaceutical products, clinical samples, and scientific research [9], [10].

b. Physics Principles

Spectrophotometric methods are based on the Beer-Lambert Law and are used to analyze various media, including biological tissues. The law defines that the totality of light emitted by a sample can decrease due to the number of absorption materials in its trajectory (concentration), the distance that light must go through (optical path distance), and the probability that the photon in the particular wave amplitude can be absorbed by the material (extinction coefficient) [11].

Lambert-Bourger law is derived from Beer-Lambert law and can be expressed in (1), which relates to the light absorption of an optically diluted homogenous medium and its thickness,

$$\frac{dI}{I} = \mu_a dl. \tag{1}$$

Where I represents the intensity, l the distance, μ_a the absorption coefficient and dl is a successive layer of the absorbent medium. Transmitted light intensity through the distance l is described by (2)

$$I = I_0 e^{-\mu_a l}, \tag{2}$$

being I_0 the initial light intensity. Another important concept in spectrophotometric theory is the absorption length (inverse of the absorption coefficient) which can be defined as the distance required for the beam of light to decrease in e^{-1} of the initial light intensity. That allows a redefinition of the transmitted light intensity shown in (3)

$$I = I_0 10^{-kl} \tag{3}$$

where k is the extinction coefficient.

In a sample, a radiation beam passes through a solution layer containing a specific absorbent species with defined thickness and concentration. Beam power is attenuated due to the

interaction between photons and absorbent particles, generating absorbance of the solution, which is a fraction of the incident radiation [12] and can be defined as (4)

$$A = kl = log\frac{I_0}{I}. \quad (4)$$

The equation above expresses the quantity of energy emitted that crosses a body in a certain amount of time. Absorbance measure is made in spectrophotometers with the aim of generating an absorption or emission spectrum. The intensity of electromagnetic radiation distribution in terms of wavelength is used to determine the characteristics of the sample [13], [14].

c. *Fluorescence of biological tissue in a single layer*

In 1852, August Beet determined that the absorption coefficient has a linear relation with the concentration of a diluted substance within the medium, represented by its concentration (c) and a constant (α), that is, as presented in (5)

$$\mu_a = \alpha c. \quad (5)$$

From the above, (2) can be rewritten such as (6)

$$I = I_0 e^{-\alpha cl} = I_0 e^{\epsilon cl}. \quad (6)$$

Where ϵ is known as the specific extinction coefficient.

When extending the definition for n substances in a sample, the total absorbance corresponds to the individual sum of the extinction coefficient times their respective concentrations times the distance. This relationship is formulated in Equation (6), which follows the same structure as Equation (7).

$$I = I_0 e^{-(\sum_{i=1}^{n} e_i c_i)l}. \quad (7)$$

The analysis of the research is focused on the study of emitted photon energy distribution. That is why, expressing the fluorescence intensity for each absorbed photon in the medium The emission characteristics, in terms of the emitted photon wavelength, are important [15] and can be defined as shown in (8)

$$\int_0^\infty F_\lambda(\lambda F)d\lambda F = \Phi_F \quad (8)$$

where Φ_F is the quantum yield, $F_\lambda(\lambda F)$ is the fluorescence emission spectrum function that reflects the probability distribution of different transition vibratory levels from state S_1 to state S_0. The emission spectrum is characterized by each fluorophore in the biological tissue.

In a practice sense, the fluorescence intensity $I_F(\lambda(F))$ measured at a certain wavelength $\lambda(F)$ is proportional to $F_\lambda(\lambda F)$ and to the number of photons that are absorbed at a excitation wavelength λ_E. It is convenient to replace the number of absorbed photons for the absorption intensity $I_A(\lambda_E)$, which is defined as the difference between intensities of incident $(I_o(\lambda_E))$ and transmitted $(I_T(\lambda_E))$ light. In that sense (9),

$$I_A = I_o(\lambda_E) - I_T(\lambda_F). \quad (9)$$

From the above, fluorescence intensity can be represented like in (10)

$$I_F(\lambda_E, \lambda_F) = kF_\lambda(\lambda_F)I_A(\lambda_E), \quad (10)$$

Then, by using (6), the above expression can be rewritten as (11):

$$I_F(\lambda_E, \lambda_F) = kF_\lambda(\lambda_F)I_0(\lambda_E)\left(1 - e^{\epsilon(\lambda_E)cl}\right). \quad (11)$$

The factor k depends on several parameters, especially in the visualization optical configuration and the bandwidth of the monochromator.

Measures of the variations of I_F in terms of λ_F, for a set excitation wavelength, reflects the changes in $F_\lambda(\lambda_F)$ and then, provides the fluorescence spectrum.

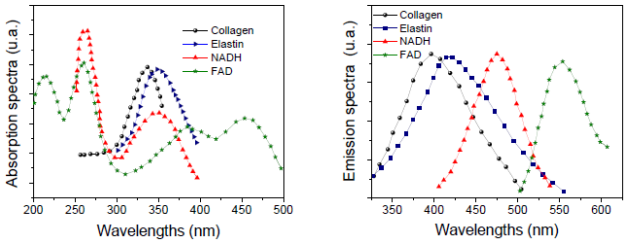
Equation (11) can be modified to obtain a less complex expression using the expansion of exponential series $1 - e^{\epsilon(\lambda_E)cl} = \epsilon(\lambda_E)cl + \frac{(\epsilon(\lambda_E)cl)^2}{2!} + \cdots$, gettingin like (12)

$$I_F(\lambda_E, \lambda_F) = kF_\lambda(\lambda_F)I_0(\lambda_E)\epsilon(\lambda_E)cl. \quad (12)$$

The relation above allows to observe the fluorescence intensity is proportional to the concentration at a low absorbance and then, the linear variation is lost with the absorbance increase. Additionally, when fluorescence spectroscopy is used to make quantitative evaluation of the fluorophore's concentration, the proportionality between fluorescence and concentration intensity, only diluted solution must be taken into account.

IV. RESULTS AND DISCUSSION

The fluorophores from the cervix tissue that contribute to the emission fluorescence signal under light excitation of 337,1 nm are collagen, elastin, NADH and flavins [16]. Figure 2 shows emission and absorption spectrum for each fluorophore in the cervix tissue. Spectrum were obtained from spectroscopy measurements and the following signal processing with gaussian fit. Figure 2a shows absorption spectrum between 200 and 500 nm, and Figure 2b shows emission spectrum between 300 and 600 nm.



a) Absorption spectrum b) Emission spectrum

Fig. 1. Spectrum with gaussian fit for each fluorophore (collagen, elastin, NADH and flavins) in the cervix tissue.

From the previous spectrum, different statistical and geometrical characteristics were extracted and are shown in Table I. There, λ_{kx} and λ_{km} refer to wavelength in the central absorption and emission spectrum respectively. I_{kx} and I_{km} are the absorption and emission intensities, respectively. W_{kx} and W_{km} corresponds to the width at mid height of each curve in the absorption and emission spectrum, respectively.

TABLE I
EXTRACTED CHARACTERISTICS FROM ABSORPTION AND EMISSION SPECTRUM OF FLUOROPHORES IN THE CERVIX

	Absorption			Emission		
Fluorophore	λ_{kx}	I_{kx}	W_{kx}	λ_{km}	I_{km}	W_{km}
Collagen	336.35	1	34.85	393.85	1	60.69
Elastin	352.03	1	46.40	405.48	1	73.08
NADH 1st peak	262.61	1	25.8	474.28	1	55.42
NADH 2nd peak	345.51	0.45	54.41			
Flavine 1st peak	260.17	1	28.77	557.44	1	65.51
Flavine 2nd peak	387.20	0.45	112.29			
Flavine 3rd peak	457.57	0.5	100.58			

Based on data from Table I, contribution factor for each fluorophore at excitation wavelength ($\lambda_x = 337.1nm$) and emission wavelength ($\lambda_m = 457.8nm$) are extracted and denoted as: CF_{kx} and CF_{km}. Equations (13) and (14) show the expression of the previous values following the definition of Beer-Lambert law.

$$CF_{kx} = I_{kx} e^{-2\left(\frac{\lambda_x - \lambda_{kx}}{W_{kx}}\right)^2} \quad (13)$$

$$CF_{km} = I_{km} e^{-2\left(\frac{\lambda_m - \lambda_{km}}{W_{km}}\right)^2} \quad (14)$$

where k depends on each fluorophore: Collagen: $k = 1$, Elastin: $k = 2$, NADH: $k = 3$, Flavins: $k = 4$.

Combining (7) and (4), total spectrum absorption with fluorophores contribution can be determined by (15) and (16),

$$A_x = \sum_{k=1}^{4} \mu_{ak} c_k CF_{kx}, \quad (15)$$

$$A_m = \sum_{k=1}^{4} \mu_{ak} c_k CF_{km}. \quad (16)$$

Where c_k represents the contributions of each fluorophore, which are unknown variables in the model and that should be calculated to contribute to the research of normal and pathological cervical tissue.

Then, total absorbance and transmission in wavelength range of 200 to 700 nm are calculated considering steps of 0.3nm, which fits with the spectrometer resolution used for the in-vivo measures. That way, contribution factors with wavelength function $CF_{k\lambda}$ are calculated

$$CF_{k\lambda} = I_{kx} e^{-2\left(\frac{\lambda - \lambda_{kx}}{W_{kx}}\right)^2}. \quad (17)$$

Using the contribution factor, it results that total absorbance and transmittance can be expressed as in (18) and (19),

$$A_\lambda = \sum_{k=1}^{4} \mu_{ak} c_k CF_{k\lambda}, \quad (18)$$

$$T_\lambda = 10^{-A}. \quad (19)$$

From those contributions, fluorescence emission intensity (I_m is calculated in (20) due to each fluorophore in the cervix tissue

$$I_{tm} = \sum_{k=1}^{4} I_k \, c_k 10^{-A_\lambda} 10^{-A_x} e^{-2\left(\frac{\lambda - \lambda_k}{W_k}\right)^2} - I_{tr}. \quad (20)$$

Where I_k, λ_k, and W_k are intensity, central wavelength, and width at mid high of the emission peaks of each fluorophore from cervix tissue, respectively.

Additionally, I_{rr} shows in (21) is a Raman band dispersion of water and an adjustment variable inside the system

$$I_{tr} = c_{rr} I_{rr} 10^{-A_\lambda} 10^{-A_x} e^{-2\left(\frac{\lambda - \lambda_{rr}}{W_{rr}}\right)^2}. \quad (21)$$

I_{rr}, λ_{rr}, W_{rr}, and c_{rr} are intensity, central wavelength, width at mid height and the contribution to dispersion band, respectively. For obtaining the parameters and their dependencies on fluorophore, each filtered and averaged spectrum was fitted using the mathematical model developed in this research, which simulates the characteristic fluorescence spectrum through (13), (14) y (20). This model is based on a sum of Gaussian bands, each representing the contribution of a specific fluorophore to the processes of absorption, excitation, emission, and transmission described throughout the theoretical development.

The fitting process employs a nonlinear least squares method to extract a set of spectral features from the fluorescence data, including fluorescence intensities, full width at half maximum (FWHM), central wavelengths, and relative contributions of each endogenous fluorophore (such as collagen, elastin, NADH, and flavins) present in the cervical tissue. This procedure is applied individually to each measurement point obtained from the spectral fluorescence data collected on cervical tissue samples. Figure 3 shows the adjustment. The spectrum shows similar shapes that the ones on the literature [17].

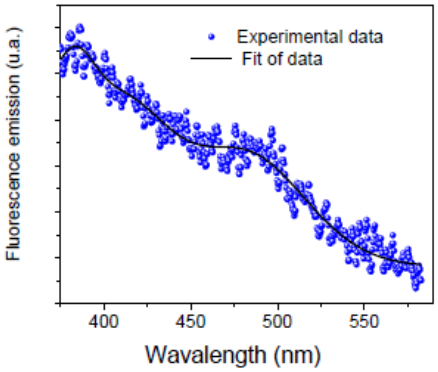
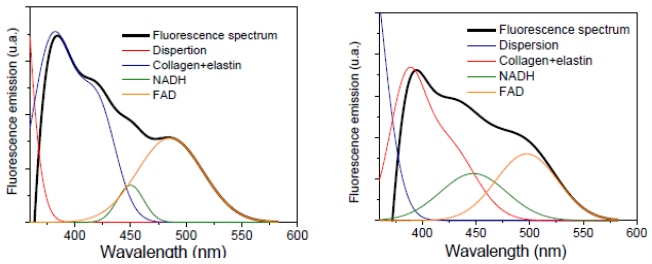


Fig. 3. Original fluorescence spectrum and adjustment with the mathematical model.

The correlation coefficients R and R^2 are calculated as normalized measures of the relationship between the variables representing the filtered and averaged spectrum and the fitted spectrum. Based on these values, the spectra corresponding to analysis points with a correlation index below ***0.9*** are discarded.

Applying the optical fluorescence spectroscopy technique, an initial test was done in normal and pathological cervical tissue of 50 patients between 17 and 60 years old. To obtain the spectrum from spectral tissue information, results from the patient's histopathology were used with the idea to find the range of each category: normal and pathological. As shown in Figure 4, there exist a notable separation between the normal and pathological spectrum, as well as the differences between maximum and minimum intensities.



a) Normal spectrum b) Pathological spectrum

Fig. 4. Spectrum with gaussian fit for each fluorophore: collagen, elastin, NADH, and flavins.

Now, Table II shows the results from simulation process using the proposed method, where parameters for Equation 20 are obtained from the patient's previous classification, followed by the classification in normal and pathological, and the extraction of the mean and standard deviation to register I_k, λ_k, W_k, and c_k. It is important to notice that collagen decrease in epithelial cells that preserve the cell structure produce an increase on NADH levels, altering normal homeostasis of the epithelium. Biological changes are analyzed and recognized using fluorescence emission spectroscopy, showing the difference between normal and pathological cervical tissue.

TABLE II
PARAMETERS OBTAINED WITH THE MATHEMATICAL MODEL, MEAN AND STANDARD DEVIATION (SD) FOR NORMAL AND PATHOLOGICAL TISSUE.

		Normal		Pathological	
Parameter	Fluorophore	Mean	SD	Mean	SD
I_k	Collagen	0.613	0.074	0.539	0.068
	Elastin	0.672	0.110	0.586	0.129
	NADH	0.588	0.107	0.542	0.186
	Flavins	0.689	0.174	0.597	0.177
λ_k	Collagen	382.878	3.615	384.530	5.716
	Elastin	417.023	5.489	415.874	6.252
	NADH	459.613	17.847	456.316	17.403
	Flavins	498.730	19.411	500.228	16.989
W_k	Collagen	35.146	10.738	31.765	11.383
	Elastin	47.541	11.877	43.936	17.876
	NADH	47.794	18.571	45.351	17.456
	Flavins	62.418	14.706	58.517	16.521
c_k	Collagen	3.590	1.146	2.537	1.119
	Elastin	3.425	0.975	2.193	0.913
	NADH	5.049	1.896	3.933	1.268
	Flavins	5.785	2.220	4.483	1.983

V. CONCLUSION

Fluorescence spectral information obtained from the technique implementation and the mathematical model developed in the research, suggest that contributions in the cervix tissue such as collagen, elastin, NADH, and flavins. The mathematical model implemented allowed to correlate the fluorophores contributions in each spectrum. In normal tissue, the collagen contribution is higher than the NADH contribution, while in pathological tissue, the NADH contribution is higher than the collagen one. The previous one is a characteristic that makes possible the identification of normal and pathological tissue. There is evidence that the combination of fluorescence spectroscopy with the adjustment model with gaussian decomposition can be an alternative tool to support medical diagnosis and recognition of intraepithelial damage in cervix tissue.

ACKNOWLEDGMENT

The author gratefully acknowledges the financial support of MinCiencias. This work was also helped by the research group of Magnetismo y Materiales Avanzados of Universidad Nacional de Colombia sede Manizales, the group of Cáncer de Cuello Uterino y Cáncer de Mama at Universidad de Caldas and the group Automática at Universidad Autónoma de Manizales.

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