Communications

Optimal Visual Perception and Detection of Oral Cavity Neoplasia

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***Abstract*—The most common way to detect disease is by visual inspection of the suspect tissue. However, the human eye is not optimized for this task because the perceived spectrum of light is divided into three channels, all of which have overlapping spectral sensitivity curves. Here, we present new methods to optimize visually perceived contrast based on spectral differences between normal and abnormal tissue. We apply these methods to the perception of fluorescence emission from the oral cavity. Abnormalities in the oral cavity are optimally perceived when the excitation is between 420–440 nm. To optimally visualize fluorescence at 340-nm excitation, the emission should be observed through a blue bandpass filter transmitting light at 430 nm.**

***Index Terms*—Autofluorescence, color difference, diagnosis, ideal observer, oral cavity, visual system.**

I. Introduction

Screening for precancerous changes of epithelial tissue is highly effective and necessary to lower mortality and morbidity [1], [2]. In general, if cancer is detected in its very early stages, it is almost always curable. For tissues that can be visualized, such as the cervix, skin, and oral cavity, the first step of cancer screening is the visual inspection of the tissue by a trained physician or nurse practitioner. However, our eyes are not optimized to detect disease. We only perceive a fraction of the possible spectral contrast because the eye's photoreceptors have broad and overlapping sensitivity in the visible spectral range [3]. Physiological modeling of perception is necessary to evaluate whether contrast improvement is possible by optimization of illumination and observation conditions. In this paper, we apply physiologic modeling to optimize perceived contrast between normal and abnormal oral cavity.

Normally, we observe reflected white light because this is the dominating light-tissue interaction. It is also possible to observe tissue autofluorescence where optical contrast between normal and cancerous tissue may be significantly greater [4]. Tissue autofluorescence originates from structural proteins (collagen and elastin), from the metabolic cofactors NAD(P)H and FAD, and from aromatic amino acids and porphyrins [5], [6]. Fluorescence is of particular interest because spectral changes may reflect changes in metabolic activity.

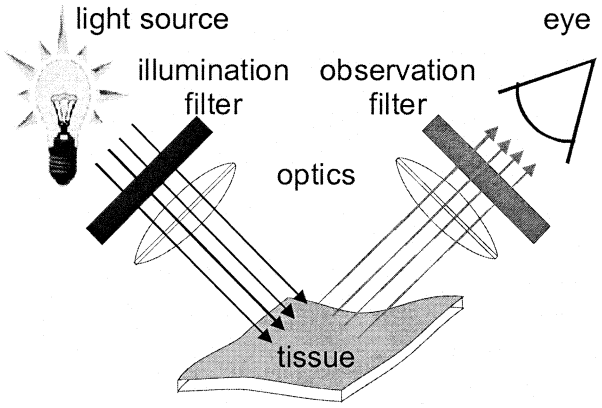

Fig. 1. Schematic diagram for optical tissue interrogation using fluorescence.

A simple device for optimized visual examination of tissue is described in Fig. 1. It consists of a standard white light source, such as a Xenon lamp, that is filtered to create illumination light at desired wavelengths. Tissue is illuminated through a fiberoptic illuminator or optical lenses and observed either directly by the eye or through magnification optics. The important additions for contrast optimization are the illumination and observation filters which are placed into the optical beam paths. Bandpass filters generate light for fluorescence excitation whereas long-pass or bandpass filters are used to observe fluorescence. These filters need to be optimized to yield maximal visual contrast. Here, we explore both color difference calculations and physiological models to quantify this contrast. We evaluated three different methodologies to measure visually perceivable differences of fluorescence spectra from precancerous and cancerous tissue and adjacent healthy tissue of the oral cavity.

Understanding color vision was a major research effort in the 20th century and continues to this day. The Commission International de l'Eclairage (CIE) [7] defined a standard system in which all visible colors could be unambiguously represented by three chromaticity coordinates. For color matching measurements, this non-Euclidian color space needs to be mapped to a more uniform space [8]. Two spaces are investigated here: the CIELAB and CIELUV space.

Optical properties of the eye are still investigated with physiological experiments to determine the characteristics of the different types of photoreceptors in the eye. Models based upon the ideal observer theory can simulate the vision process and explain perception at the level of the receptors [9].

Our results show that significant contrast enhancement is possible with optimal selection of illumination and observation filters for fluorescence-based detection of oral cancer and precancer.

II. Methods

A. Clinical Data

The dataset used in this study was extensively described by Heintzelman *et al.* [10]. Here, data are used from a subset of 11 patients in whom fluorescence spectra were measured from both normal and neoplastic sites in the oral cavity. In this group of patients,

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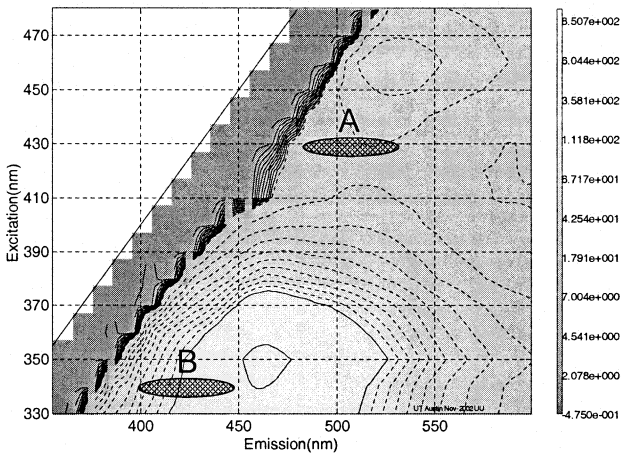

Fig. 2. Typical fluorescence EEM of cancerous oral cavity. Ordinate is the excitation wavelength and abscissa the emission wavelength. Contour lines connect points with the same fluorescence intensity. Excitation and observation conditions marked with A and B are referred to in the text and Fig. 4.

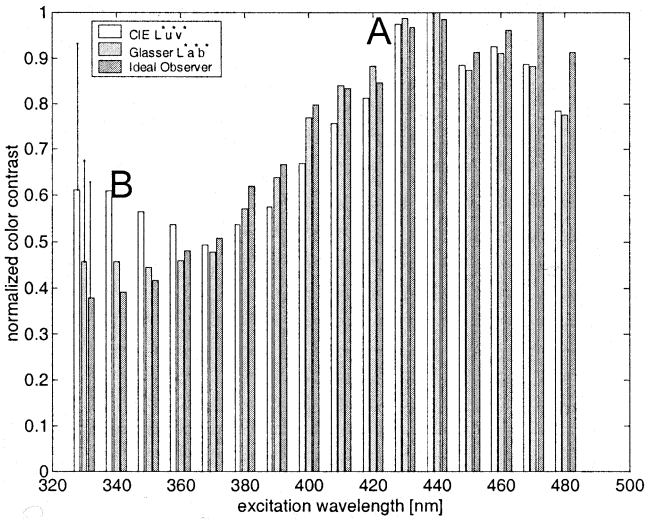

Fig. 3. Comparison of perceived contrast between normal and neoplastic oral cavity at different excitation wavelengths with observation of the whole emission wavelength range. Average contrast between fluorescence emission spectra of normal and abnormal oral cavity is plotted. Contrast values are calculated using three different methods. At 330-nm excitation, the error bars represent one standard deviation. Contrast improvement between excitation at 440 (A) and 340 (B) is statistically significant ($p < 0.01$).

spectra were measured from 19 normal sites, seven precancerous sites, and eight sites with cancer. For the purpose of analysis, spectra from precancerous and cancerous sites were considered as a single group (abnormal). From these data all possible pairwise combinations of normal and abnormal spectra within a single patient were created resulting in 19 pairs. Eleven of these pairs compared normal spectra with precancerous spectra. The spectroscopic device used to acquire fluorescence excitation emission matrices (EEMs) is described in detail by Zuluaga *et al.* [11]. It measures emission spectra at 18 different excitation wavelengths, ranging from 330 to 480 nm. For the analysis presented here, the emission range was limited from 400–590 nm.

An example fluorescence EEM is presented in Fig. 2. Emission wavelength is plotted on the abscissa and the excitation wavelength on the ordinate. Contour lines connect points of equal intensity. This cancerous site emits light at 350/450 nm (excitation/emission) which is consistent with NAD(P)H and structural proteins and at 450/530 nm which is consistent with FAD and structural proteins. Hemoglobin absorption of the fluorescence light at 420 nm can be observed as valleys in emission and excitation direction.

B. Contrast Calculation

In this investigation, three different contrast calculation methods were applied to calculate the perceived visual contrast between normal and abnormal tissue. Since we were only interested in relative color differences, all emission spectra were normalized to either the maximum of the normal or abnormal spectrum, whichever was greater. This is equivalent to assuming that we have sufficient neural stimuli so that the light level does not affect the color perception.

Two of the three calculation methods are based on the CIE specifications of the standard observer of colorimetry [7]. Spectra from normal and abnormal sites are converted to the appropriate values in the tristimulus space. The color difference is then calculated by measuring the Euclidian distance between the two points. Points which are further apart correspond to higher perceived contrast.

The color spaces used here were the $L^*a^*b^*$ (CIELAB) and the $L^*u^*v^*$ (CIELUV) system. In the $L^*a^*b^*$ system, L^* represents lightness, positive a^* redness, negative a^* greenness, positive b^* yellowness, and negative b^* blueness. In the CIELAB system, color difference was calculated using the method described by Glasser *et al.* [12] and in the CIELUV system with the method defined by CIE [13]. For historical reasons, both the CIELAB and the CIELUV color space are recommended to calculate color differences.

The third method to calculate contrast differences is based on a physiological model and makes use of ideal observer analysis. The calculated contrast values represent the performance of the eye as a three-channel photodetector, taking the sensitivity of the red, blue, and green cones [14] and the transmittance of the ocular media [15] into account. The contrast based upon the difference in the total radiance (intensity) and wavelength distribution (color) was calculated according the method of Geisler [9]. This theory evaluates the performance of the observer at the level of the photopigments in the human cone photoreceptors, whereas the CIE models are based on the contrast perceived by the brain.

The three methods were independently applied to the data set. The average contrast difference between normal and abnormal spectra from all 19 spectral pairs was calculated separately for each excitation wavelength (330 to 480 nm) assuming the entire emission spectrum was viewed. This is equivalent to an observer wearing long-pass filters to block the reflected excitation light from entering the eye. Values from the same excitation wavelength were then averaged and, in a second step, compared with other observation conditions using the Student's t-test.

In addition, fluorescence can be viewed with bandpass filters of variable width and center wavelength. For this level of optimization, only one method was chosen: the CIELAB method of Glasser *et al.* [12]. We calculated average contrast values for bandpass-filtered emission with bandwidths ranging from 20 to 100 nm in 10-nm steps. The center wavelength of the bandpass filter was shifted over the measured emission spectra in 10-nm steps. We investigated whether any of these spectrally limited stimuli are able to produce higher contrast value than the full fluorescence emission spectrum.

III. Results

A. Observation of Entire Emission Epectrum

Results from the analysis of visual examination of the full fluorescence emission spectrum are shown in Fig. 3. The averaged contrast values are plotted at each excitation wavelength for all three contrast calculation methods. At 330-nm excitation, the standard deviation of

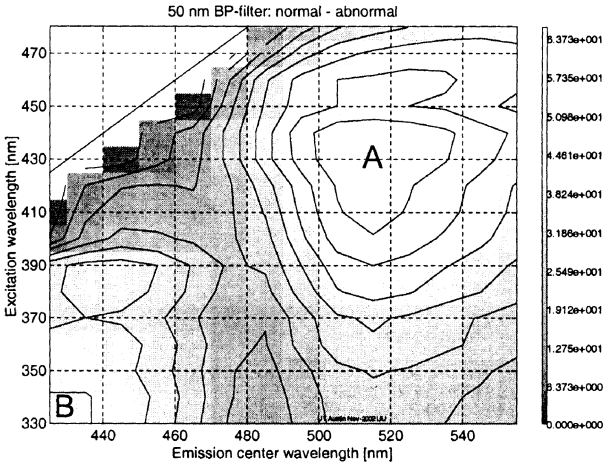

Fig. 4. Average contrast between normal and abnormal oral cavity at excitation wavelength versus center wavelength of the bandpass emission filter. The bandpass of the emission filter was 50 nm. Contrast in area A is 15% larger than at 430-nm excitation and full emission spectrum observation (Fig. 2). Contrast in area B is 30% lower than in area A.

the 19 sample pairs is also shown. All three computational methods reveal similar trends and differences are small compared with the standard deviation. The two methods based on the CIE standard observer show highest contrast at 440-nm excitation. Results from the ideal observer theory also peak near this wavelength but the highest contrast was calculated at 470-nm excitation. In general, excitation between 420–470 nm produces high perceivable contrasts. Maximal contrast calculated with the method of Glasser *et al.* [12] at 440-nm excitation (location A) is significantly higher (factor of 2, $p < 0.01$) than minimal contrast at 340-nm excitation (location B).

B. Optimized Observation and Excitation Conditions

One method was chosen to further optimize perceived contrast with bandpass filtered observation. The method of Glasser *et al.* in the CIELAB color space is ideal for this purpose because the color space transformation does not involve division of intensities which can become zero when the filter bandwidth is small.

Fig. 4 shows an example of optimized observation conditions through a 50-nm wide bandpass filter. Similar to Fig. 2, the center wavelength of the observation filter is plotted on the abscissa and the excitation wavelength on the ordinate, and contour lines connect points of equal contrast. Areas with a local contrast increase are observed in all configurations. They are at 430/515 nm (excitation/emission wavelength, location A, blue excitation), 410/510 nm, 460/520 nm, 330/430 nm (location B, UV excitation), and 380/440 nm, and listed here in order of decreasing contrast contribution. The best results in all simulated observation configurations were fluorescence excitation at 430 nm and observation of the emitted light through a 50-nm-wide band at 515 nm (location A in Figs. 2 and 4). A larger or smaller observation bandwidth resulted in reduced contrast (3%–8%), however, these differences were not statistically significant ($p > 0.3$). At 430/515 nm (blue excitation), the contrast increased with all bandpass filters compared with no bandpass filtering. However, none of these increases are statistically significant $p >= 0.2$). Maximal increase was 15% (location A). In contrast, observing fluorescence through a bandpass filter (bandwidth $<$ 100 nm) at 340/430 nm (location B) is advantageous because contrast is increased between 50% and 75% ($p < 0.03$). However, this optimized contrast is still 30% below the highest achievable contrast at 430/515 nm (location A).

It is expected that contrast between normal and precancerous tissue is lower than between normal and cancerous tissue. We repeated our analysis to quantify this reduction by excluding the cancerous samples. The analysis of 11 paired samples showed contrast maxima at the same observation conditions as was found previously. The decrease at the best observation condition (location A) was 25%, however, the decrease was not statistically significant ($p = 0.14$).

IV. Discussion and Conclusion

In this paper, we evaluated the use of color difference formulae and of a physiological model of human photoreceptor responses for optimizing the perception of oral cavity disease. All efforts were focused on the observation of tissue fluorescence. However, the methodologies are universal and can also be used to analyze reflected light.

We demonstrated that selecting appropriate excitation wavelengths for visual fluorescence observation increases the perceived contrast by a factor of two. The best excitation wavelengths for investigation of oral cavity neoplasia are between 420 and 440 nm. The use of bandpass filters for the observation of fluorescence emission can potentially increase the perceivable contrast between normal and abnormal tissue. However, we could not demonstrate statistical significance at the best excitation wavelength. An observation of the emitted fluorescence through a bandpass filter of 50 nm centered at 515 nm provides color stimuli that are best distinguishable by the human visual system. The optimally observed center wavelength at 515 nm is in the green spectral range which is ideally located in the middle of the sensitivity maxima of the three cone photoreceptors. Our results confirm that the contrast is reduced by 25% when observing normal versus precancerous samples compared with observations that include cancerous samples. However, the decrease was not statistically significant.

In all calculations, it was assumed that the power of the excitation light source is not limited and that the color photoreceptors are sufficiently activated. However, visual fluorescence observation is a low-light level process and the reduction of the observation bandwidth will result in lesser neural stimulations. Fluorescence intensities at ultraviolet excitation (e.g., 340 nm) can be one to two orders of magnitude stronger (see [16] and Fig. 2) than at blue excitation. We found that by using an observation bandpass filter that transmits blue light at 430 nm, we can significantly increase the perceivable contrast and compensate for the otherwise poor contrast at this excitation wavelength. Further research is necessary to simulate low-light level observation using an extended model of color visions such as the CA90 model [17].

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