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Modeling of Optical Properties of Normal and Tumor Tissue Using Reflectance Spectra for Appropriate Dosimetry in Photodynamic Therapy

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Abstract: The evolution of photodynamic therapy (PDT) to a fully developed treatment modality requires the development of appropriate dosimetry to ensure proper quality control during treatments. The parameters measured for PDT quality control are drug accumulation and penetration depth. In this study, a model has been developed based on reflectance spectroscopy to help understanding light propagation from light delivery system to tissue and vice versa. This model can be used to determine the depth of tissue necrosis during PDT and to evaluate and improve the dosimetry.

Key words: Photodynamic therapy, reflectance spectroscopy, modeling, dosimetry, penetration depth, reduced scattering coefficient, absorption coefficient

INTRODUCTION

Photodynamic therapy (PDT) is a technique for treating a variety of malignant and nonmalignant conditions based on the use of light-activated drugs (photosensitizers). Typically, the photosensitizer is administered either systemically (intravenously or orally) or topically to the tissue to be treated (Dolmans *et al*., 2003). After allowing time for uptake of the photosensitizer by the target tissue, light of an appropriate wavelength is used to activate the drug. This results in the photoproduction of one or more cytotoxic agents, leading to the intended cellular and tissue effects. Drug and light doses are parameters that can be appropriately changed to improve the outcome of PDT procedure (Wilson *et al*., 1997). Therefore, to estimate and predict the appropriate dosage, the optical properties of the tissue needs to be determined for successful treatment. In this study, a model has been developed based on reflectance spectroscopy to determine the optical properties of tissue that influence the depth of tissue necrosis and have a primary effect on the depth of treatment. The ability to determine two parameters, the reduced scattering coefficient (μ'_s) and the absorption coefficient (μ_a), with one spectral reflectance measurement is only possible because of the spectral nature of the tissue components. For this, in present model, we assume that the tissue absorption coefficient is composed of absorption from dry tissue (μ_a^{dry}), water (μ_a^{water}), oxy-and deoxy-blood (μ_a^{oxy} and μ_a^{deoxy}) and assume that the reduced scattering coefficient behaves as $a\lambda^{-b}$. Also, we use a fitting routine to determine unknown coefficients of present model. As with any fitting routine, starting with the appropriate initial values for the fitting parameters helps avoiding local minima which leads to incorrect results in the minimization routine. We have compared the results of present model with those obtained experimentally as reported by other researcher. The results show that present model provides a valuable tool for predicting the optical properties of tissue.

PDT AND TISSUE NECROSIS

A simple rule for PDT dosimetry that specifies the depth of tissue necrosis during PDT was proposed by Jacques (1989, 1992, 1998). The depth of tissue necrosis is related to the natural logarithm of treatment light as it penetrates into the tissue and is given by:

$$z_{necrosis} = \delta \ln\left(\frac{E_0 tk\varepsilon Cb\Phi f}{R_{th}}\right) \quad (1)$$

Where:

E_0 = Irradiance of treatment light onto the tissue surface (W cm^{-2})
t = Exposure time for treatment light (sec)
δ = Optical penetration depth of treatment light (cm)
k = Augmentation of light at surface due to backscattering from tissue (dimensionless)
$z_{necrosis}$ = Depth of the margin for zone of necrosis (cm)
ε = Extinction coefficient of photosensitizing drug (cm^{-1}/(mg/g)

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C = Concentration of photosensitizing drug (mg g^{-1})
b = Photons per joule of light energy at treatment wavelength (ph J^{-1})
Φ = Quantum efficiency for generation of oxidizing species (dimensionless)
f = Fraction of oxidizing species that attack critical sites that contribute to cell death (dimensionless)
R_{th} = Threshold concentration of critical oxidation attacks for cell death (moles L^{-1})

The practical consequence of Eq.1 is that the optical properties of tissue influence δ and have a primary effect on the depth of treatment. The tissue optical properties that influence light transport in tissue are the absorption coefficient, μ_a (cm^{-1}) and the reduced scattering coefficient, μ'_s (cm^{-1}), (Star, 1995; Wilson and Jacques, 1991; Star *et al*., 1988). The optical penetration depth, δ (cm) is related to μ_a and μ_s' :

$$\delta = \frac{1}{\sqrt{3\mu_a(\mu_a + \mu'_s}} \approx \frac{1}{\sqrt{3\mu_a \mu'_s}} \quad (2)$$

The value of μ'_s is usually at least 10-times greater than the value of μ_a in the diffusion limit. If μ'_s is comparable to or less than μ_a, then diffusion theory no longer holds and δ is equal to $1/\mu_a$. Here, we will assume that μ'_s exceeds μ_a. A change in the blood content of a tissue will cause a proportional change in μ_a and δ will change as the square root of the change in blood content (Douplik *et al*., 2000). Since the PDT treatment zone is proportional to δ, it is expected that treatment zone will vary as much as the square root of the degree of tissue inflammation (Amelink, 2005; Dickey *et al*., 2004).

Experimental determination of tissue optical properties has been proposed using different methodologies. Integrating sphere photometry, frequency domain diffuse reflectance, time domain diffuse reflectance, optoacoustic and spatially resolved steady-state diffuse reflectance are among the most widely used methods (Doornbos *et al*., 1999). In this study, we present a spatially resolved steady-state diffuse reflectance model which is based on using two fibers (one for transmitting and one for receiving light) for determining the optical properties. The model relies on the spectral characteristics of the tissue chromophores (water, dry tissue and blood) to determine the absorption coefficient and on a simple wavelength dependence expression $\mu'_s = a\lambda^{-b}$ (Bargo *et al*., 2003) for the determination of the reduced scattering coefficient. Advantages of using this method are the low cost of the experimental set up and the simplicity of the measurements.

MODELING OF TISSUE REFLECTANCE WITH THE SPECTRAL MODEL

In present study, tissue absorption was modeled as a linear combination of water (μ_a^{water}), a background spectrum for dry bloodless tissue (μ_a^{dry}) and a variable blood volume fraction (f_v) of oxygenated and deoxygenated whole blood (μ_a^{oxy}), (μ_a^{deoxy}) at an oxygen saturation (SO_2).

Tissue scattering can be represented by the expression $a\lambda^{-b}+c\lambda^{-d}$ (Amelink *et al*., 2005, 2003). The term $a\lambda^{-b}$ mimics the Mie scattering from larger tissue structures such as collagen fiber bundles, mitochondria, nuclei and cells. The term $c\lambda^{-d}$ accounts for Rayleigh scattering at shorter wavelength from collagen fibril fine structure, small membranes and other ultrastructure on the 10-100 nm scale (Saidi *et al*., 1995). The Rayleigh scattering factor was neglected in our modeling because the present spectra were acquired above 500 nm and were not sensitive to Rayleigh scattering. The absorption coefficient μ_a and reduced scattering coefficient μ'_s were specified as:

$$\mu_a(\lambda) = \mu_a^{dry}(\lambda) + f_w\mu_a^{water}(\lambda) + f_v\,(SO_2\,\mu_a^{oxy}(\lambda) + (1-SO_2)\,\mu_a^{deoxy}(\lambda) \quad (3)$$

$$\mu_s(\lambda) = a\lambda^{-b} \quad (4)$$

$$\mu_a^{dry}(\lambda) = A\exp(-B\lambda) \quad (5)$$

Where:

$\mu_a(\lambda)$ = Total absorption coefficient of tissue *in vivo*, (cm^{-1})
$\mu_a^{dry}(\lambda)$ = Absorption coefficient of dry bloodless tissue (cm^{-1})
$\mu_a^{water}(\lambda)$ = Absorption coefficient of pure water (cm^{-1})
$\mu_a^{oxy}(\lambda)$ = Absorption of fully oxygenated blood (45% hematocrit) (cm^{-1})
$\mu_a^{deoxy}(\lambda)$ = Absorption of fully deoxygenated blood (45% hematocrit) (cm^{-1})
fw = Volume fraction of water (dimensionless)
fv = Volume fraction of 45% hematocrit blood in tissue (dimensionless)
SO_2 = Oxygen saturation (dimensionless)
A = Amplitude constant for $\mu_a^{dry}(\lambda)$ (cm^{-1})
B = Rate constant for $\mu_a^{dry}(\lambda)$ (nm^{-1})
$\mu'_s(\lambda)$ = Reduced scattering coefficient of tissue *in vivo* (cm^{-1})
a = Factor that characterizes magnitude of scattering (cm^{-1})
b = Factor that characterizes wavelength dependence of scattering (dimensionless)
λ = Wavelength (nm)

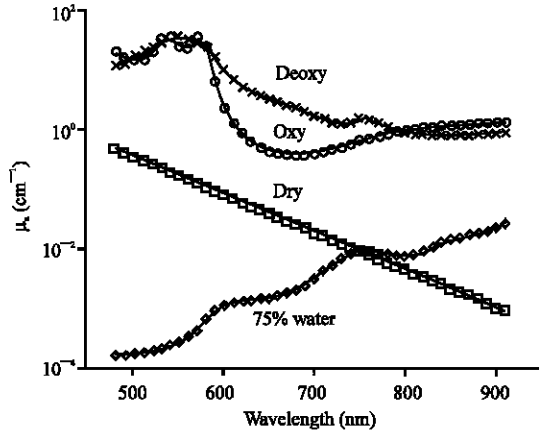

Fig. 1: Spectra of tissue chromophores (Bargo *et al*., 2003)

Typical spectra for μ_a^{dry}, μ_a^{water}, μ_a^{oxy} and μ_a^{deoxy} for whole blood at 45% hematocrit are shown in (Fig. 1).

DETERMINATION OF MODEL COEFFICIENTS

Values of a, b, A, B, blood fraction (f_v) and blood oxygen saturation (SO_2), were determined by a least square minimization routine described below:

- Variables a, b, f_v, A and B were initialized
- The parameters μ_a and μ_s were determined using Eq. 3-5 for isobestic wavelengths (500, 530, 545, 570, 584 and 796 nm) and using SO_2 set to 1
- Reflectance measurements for samples (M_s) could be normalized, for example by the epoxy/titanium-dioxide (epoxy-TiO_2) solid standard (M_{std}). The final spectrum was the ratio M as given below:

$$M(\lambda) = \frac{M_s(\lambda)}{M_{std}(\lambda)} \quad (6)$$

- The predicted normalized measurement (pM(λ)) can be calculated from Eq. 7:

$$M(\lambda) = \frac{M_s(\lambda)}{M_{std}(\lambda)} = \frac{S(\lambda)T_s(\lambda)\eta_c(\lambda)D(\lambda)}{S(\lambda)R_{std}(\lambda)\eta_{c,std}(\lambda)D_{\eta c}(\lambda)} = \frac{Ts(\lambda)\eta_c(\lambda)}{R_{std}T_s(\lambda)\eta_{c,std}(\lambda)} \quad (7)$$

Where:

$S(\lambda)$ = Light source power (the source spectral response) (W)

$D(\lambda)$ = Detector sensitivity (the detector spectral response) (counts W)

$T_s(\lambda)$ = Optical transport into the medium and returning to the sample surface at the Collection fiber (1 cm^{-2})

$\eta_c(\lambda)$ = Collection efficiency of the optical fiber (dimensionless)

$R_{std}(\lambda)$ = Standard reflectance (0.65 at 630 nm) (dimensionless)

- The results of present model can be compared with the experimental normalized measurement from the patient (M(λ)) that obtained from experimental. The error, E, provides a good measure of how close these results are:

$$E = \sqrt{\sum_{\lambda=\lambda i}^{\lambda f}((pM(\lambda) - M(\lambda)/M(\lambda))^2} \quad (8)$$

The algorithm will be repeated until E reduces a minimum acceptable value.

- Variables a, b, f_v, A and B were update
- The process was iterated until error reached less than 0.001
- After determining the variables a, b, f_v, A and B for the isobestic wavelengths the value of b was fixed and the variables a, f_v, A and B were used as starting point to fit these variables plus the SO_2 for all the wavelengths.
- The parameters μ_a and μ_s were determined using Eq. 3-5 for all the wavelengths
- The predicted normalized measurement was calculated wavelength-by-wavelength
- The predicted normalized measurement (pM(λ)) was compared to the experimental normalized measurement from the patient (M(λ)) in a least square minimization process by minimizing the square error according to Eq. 8
- Variables a, f_v, SO_2, A and B were update
- The process iterated until error was less than 0.001

RESULTS AND DISCUSSION

Figure 2a shows the results obtained by running the spectral model and are compared with the results from reported experiments for healthy esophageal tissue. The normalized residual error [(predicted-experimental)/ experimental] is shown in Fig. 2b. Figure 3a shows corresponding results for the cancerous esophageal tissue. Experimental spectra have been received from Bargo *et al.* (2003).

The results of this model agree well with the experimental results. The residuals shown in Fig. 2 b and 3b are small for spectral ranges from 650 to 850 nm. Disagreement is noticeable in the spectra below 650 nm, as it expected, since diffusion theory fails when the

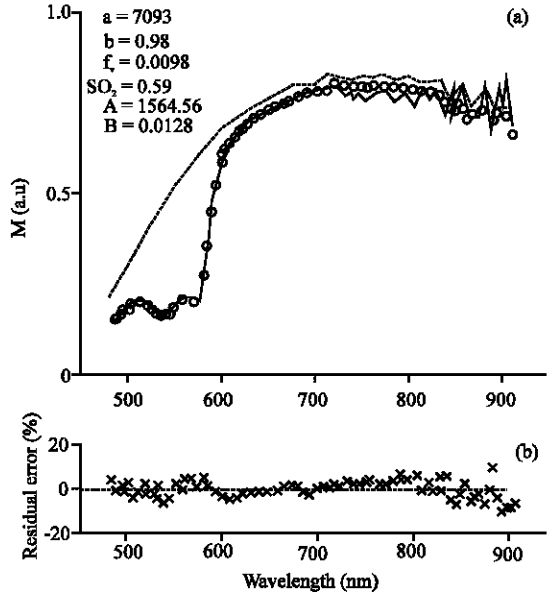

Fig. 2: (a) Normalized data for healthy esophageal tissue in comparison with the predicted values (circles) determined using the fitted parameters a, b, f_v, SO_2, A and B and Eq. 3-5 and (b) show the percentage residual error

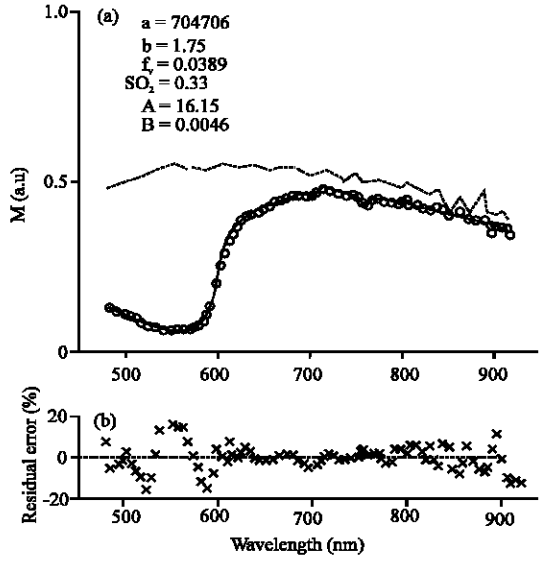

Fig. 3: (a) Normalized data for tumor in esophageal tissue in comparison with the predicted values (circles) determined using the fitted parameters a, b, f_v, SO_2, A and B and Eq. 3-5 and (b) show the percentage residual error

reduced mean free path $(1/(\mu_a+\mu_s'))$ is comparable with the source-detector separation and when μ_a is comparable to μ_s'.

CONCLUSION

In this study, we have presented a model for determining optical properties of normal and tumor tissue, based on reflectance spectroscopy. This model relies on spectral characteristics of the tissue chromophores to determine the absorption coefficient and on a wavelength dependence expression for the determination of the reduced scattering coefficient. The results of the proposed model agree well with the reported experimental results. There for the model can be used to obtain a good estimation of the optical properties of tissue that influence the depth of tissue necrosis.

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REFERENCES

Amelink, A., M.P.L. Bard, J.A. Burgers and H.J.C.M. Sterenborg, 2003. Single scattering spectroscopy for the endoscopic analysis of particle size in superficial layers of turbid media. Applied Optics, 42: 4095-4101.

Amelink, A., 2005. Monitoring PDT by means of superficial reflectance spectroscopy. J. Photochem. Photobiol. B., 79: 243-251.

Bargo, P.R., S.A. Prahl and S.L. Jacques, 2003. Collection efficiency of a single optical fiber in turbid media. Applied Optics, 42: 3187-3197.

Dickey, D.J., K. Partridge, R.B. Moore and J. Tulip, 2004. Light dosimetry for multiple cylindrical diffusing sources for use in photodynamic therapy. Phys. Med. Biol., 49: 3197-3208.

Dolmans, D.E.J.G.J., D. Fukumura and R.K. Jain, 2003. Photodynamic therapy of cancer. Nature Rev. Cancer, 3: 380-387.

Doornbos, R.M.P., R. Lang, M. Aalder, F.W. Cross and H. Sterenborg, 1999. The determination of an *in vivo* human tissue optical properties and absolute chromophore concentrations using spatially resolved steady-state diffuse reflectance spectroscopy. Phys. Med. Biol., 44: 967-981.

Douplik, A., A.A. Stratonnikov and V.B. Loshchenov, 2000. Study of photodynamic reactions in human blood. J. Biomed. Opt., 5: 338-349.

Jacques, S.L., 1989. Simple theory, measurements and rules of thumb for dosimetry during photodynamic therapy. Proc. SPIE, 1065: 100-108.

Jacques, S.L., 1992. Laser-tissue interactions: photochemical, photothermal, photomechanical. Surgical Clin., 72: 531-558.

Jacques, S.L., 1998. Light distributions from point, line and plane sources for photochemical reactions and fluorescence in turbid biological tissue. Photochem. Photobiol., 67: 23-32.

Saidi, I.S., S.L. Jaques and F.K. Tittel, 1995. Mie and rayleigh modeling of visible light scattering in neonatal skin. Applied Optics, 34: 7410-7418.

Star, W.M., J.P. Marijnissen and M.J. van Gemert, 1988. Light dosimetry in optical phantoms and in tissues: I. Multiple flux and transport theory. Phys. Med. Biol., 33: 437-454.

Star, W.M., 1995. Diffusion Theory of Light Transport. In: Optical-Thermal Response of Laser Irradiated Tissue, Welch, A.J. and M.J.C. Van Gemert (Eds.). Plenum Press, New York, pp: 131-206.

Wilson, B.C. and S.L. Jacques, 1991. Optical reflectance and transmittance of tissues: Principles and applications. IEEE J. Quantum Elect., 26: 2186-2199.

Wilson, B.C., M.S. Patterson and L. Lilge, 1997. Implicit and explicit dosimetry in photodynamic therapy: A new paradigm. Lasers Med. Sci., 12: 182-199.