Journal of Biomedical Optics

SPIEDigitalLibrary.org/jbo

Simulating light transport through skin for color prediction of port wine stain lesions: a review

Tom Lister
Philip A. Wright
Paul H. Chappell

SPIE

Journal of Biomedical Optics 17(11), 110901 (November 2012)

REVIEW

Simulating light transport through skin for color prediction of port wine stain lesions: a review

Tom Lister,[a,b] Philip A. Wright,[b] and Paul H. Chappell[a]
[a]Salisbury District Hospital, Wessex Specialist Laser Centre, Salisbury SP2 8BJ, United Kingdom
[b]University of Southampton, School of Electronics and Computer Science, University Road, Southampton SO17 1BJ, United Kingdom

Abstract. A survey of the literature is presented regarding the simulation of port wine stain (PWS) skin color. Knowledge of PWS features, such as the depths and diameters of affected vessels, is essential for informing laser treatment. These may be determined through the inverse application of a skin model. The techniques which have been applied to achieve this are analyzed in detail. Radiative transfer (RT) is found to be the preferred method of simulation. By far the most common approximations to RT are the diffusion approximations, which have been applied successfully in the past and Monte Carlo techniques, which are now the methods of choice. As the requirements for improvement of laser treatment on an individual basis continues, the needs for further work towards accurate estimations of individual optical coefficients and robust, flexible simulation techniques are identified. [DOI: 10.1117/1.JBO.17.11.110901]

Keywords: port wine stain; Monte Carlo simulation; diffusion approximation; radiative transfer theory; skin color.

Paper 12583V received Sep. 6, 2012; revised manuscript received Oct. 11, 2012; accepted for publication Oct. 16, 2012; published online Nov. 14, 2012.

1 Introduction

Port wine stains (PWS) are progressive vascular lesions of the dermis affecting around 25 million people worldwide.[1] They often constitute a significant cosmetic problem, and, if left untreated, are likely to develop nodular or hypertrophic areas which are prone to spontaneous or trauma-induced bleeding and consecutive infection.[2,3] The long-term psychological effects of PWS are documented widely but have been shown to be mitigated significantly after treatment.[4]

Although flashlamp-pumped pulsed dye laser (PDL) treatments are widely considered the treatment of choice for PWS, fewer than 20% of patients experience complete lightening using this method, whereas 20% to 30% are considered "poor responders".[5–7] It has been proposed that one reason for inadequate clinical results is that the laser parameters used are virtually identical for all PWS patients despite the commercial availability of laser systems with user-specific settings.[8,9] In order that laser treatment may be optimized on an individual patient basis, the practitioner must be aware of the vascular architecture constituting each lesion, including the number, distribution and sizes of affected vessels.[9] It is these characteristics, as well as the properties of overlying skin (such as epidermal melanin content) which constitute the color of PWS skin.[10]

The simplest method of assessing PWS color is through visual observation. However, this is both subjective and qualitative. Perceived color may be influenced by a number of factors such as ambient lighting conditions, colors surrounding the subject, eye adaptation prior to viewing and viewing geometry.[7,11] Although photographic images have been applied to determine the efficacy of laser treatment for PWS, great care must be taken to minimize the effects of variations in patient positioning, camera sensitivity and lighting during acquisition, and the quality of printing or visual display of the image.[12,13] To confound this further, communication of perceived color is difficult as, for example, most PWS skin may correctly be described as 'red' in color.

Quantitative, reproducible assessments of PWS lesions have been achieved using color measurements (for a full discussion, see Ref. 1). Color measurement devices consist of one or more optical fibers or integrating spheres which are placed in contact with the skin and through which incident and reflected light are passed. Data available from these devices may include spectral reflectance curves covering a broad spectrum, (Fig. 1), color coordinate values relating to human color perception or indices representing approximations of blood or melanin content. Once a technique restricted to the laboratory, modern handheld devices are capable of collecting skin color data instantaneously. Although care must be taken to avoid blanching during contact and to replicate the positioning of the device between assessments, color measurements have been shown to produce excellent inter- and intra-user repeatability (Fig. 1),[14,15] and have been applied successfully in the determination of laser treatment efficacy in PWS lesions.[16]

Clinically relevant, objective information may be determined from skin color measurements through the inverse application of a skin model. This method begins by creating a mathematical skin model through which light transport is simulated. Specific features of the model are then adjusted until its simulated color is in adequate agreement with the measured color of the patient's skin. These adjusted features, such as concentrations and distributions of melanin and hemoglobin, can be used to inform diagnosis or treatment. Simulations of skin color require an understanding of the optical properties of skin,[10] and must consider the prominent interactions of light. This article addresses the latter, presenting a comprehensive review and

Address all correspondence to: Tom Lister, Salisbury District Hospital, Wessex Specialist Laser Centre, Salisbury SP2 8BJ, United Kingdom. E-mail: tom.lister@soton.ac.uk.

0091-3286/2012/$25.00

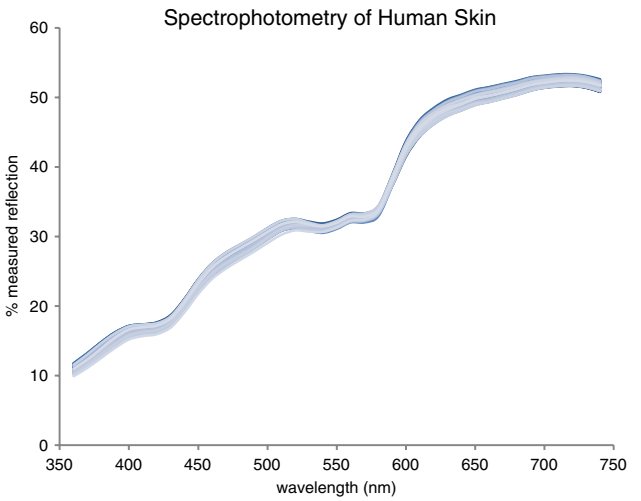

Fig. 1 Spectral reflectance of 50 consecutive measurements from the inner forearm of the first author (T. Lister) obtained using a Konica-Minolta 2600d integrating sphere spectrophotometer.

analysis of the approaches used to simulate light transport through PWS skin.

2 Skin Color

When skin is illuminated with a white light source, its color is determined by the spectral variation in reflected and backscattered light. The proportion of light reflected from the surface of skin has not been shown to vary substantially with wavelength or between individuals, and does not contribute appreciably to the color of skin.[17,18] The remaining light may be absorbed within the skin or scattered back to the surface. The proportion of backscattered light varies considerably with wavelength, pigment content and scattering properties of the skin.[10] Thus, it is this backscattered light which is predominantly responsible for the color of skin.

With regards to PWS skin, vessel number, mean diameter and depth have been shown to influence the color of the lesion.[19–22] It has been suggested that equivalent colors can be obtained through different combinations of these parameters. For example, Barsky et al. carried out an investigation involving biopsy samples from 100 facial PWS lesions.[19] They observed that the mean vessel area and total vascular area correlated strongly with color assessed using a visual comparison of the skin against a Pantone color chart. Thus, Barsky's results suggest than skin color is derived from the quantity of blood in PWS skin, independent of its distribution through the dermis. Fiskerstrand et al.[21] used the same methods of 3-mm punch biopsies on 30 patients and comparisons against a Pantene color chart. They also reported that skin color was dependent upon vascular area, but found that "pink and purple lesions were significantly deeper located than were the red lesions," and larger diameter vessels corresponded with a darkening of PWS color, from pink to purple.[20,21] Verkruysse et al. introduced a correction factor to investigate the effect of vessel diameter on PWS color through Monte Carlo simulations. They suggested that several small vessels, close to each other, may be optically equivalent to one large vessel over the yellow and blue regions of the visible spectrum. However, their simulated results showed that the proportion of red light reflected from the skin was influenced strongly when varying dermal blood fraction but only minimally when varying vessel diameter (Fig. 2).

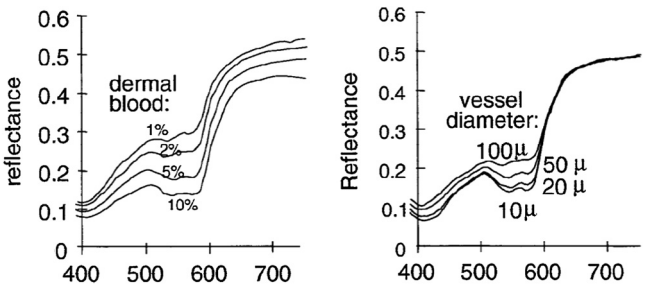

Fig. 2 Change in simulated spectral reflection with varying dermal blood concentration (left) and vessel diameter (right). With kind permission from Ref. 61.

3 Simulating PWS Skin Color

In order to accurately reproduce human skin color, and variations in color between individuals or regions, over time or as a result of a medical condition such as PWS, a simulation must account for the prominent interactions of light within skin. These interactions may be described using classical electromagnetics, based upon Maxwell's equations, whereby light is treated as a wave containing an electric component and a magnetic component. When traveling through a medium such as skin, this wave causes elements of electric or magnetic charge (e.g., electrons) to oscillate and, in turn, the oscillating elements radiate electromagnetic waves. The observed transmitted or scattered wave is a result of the summation of each of these secondary waves. The secondary waves may not have the same phase or magnitude as the incident wave and some of the energy will be lost to the charged elements; further energy is lost to the medium through destructive interference of secondary waves.

An exact calculation of the resultant wave is exceedingly complex, as it relies not only on the precise position of each charged element in the medium, but also upon the local electromagnetic environment, which is continually altered by the interaction of the wave with the medium. Instead, specific solutions to Maxwell's equations have been developed for simplified situations.

4 At the Skin Surface

The effects of surface topology on skin appearance are of considerable interest to the cosmetic[23] and computed animation[24,25] industries, as well as medicine.[26,27] These investigations are primarily concerned with differences in appearance as a result of varying viewpoints or angles of illumination. However, the majority of studies into PWS skin color consider a simple approach to approximating surface reflection. By modeling the skin surface as a perfectly smooth interface, and by assuming the superficial region of the skin can be assigned a single value of refractive index for the wavelength or wavelength range considered, the Fresnel equation may be used to estimate the relative quantities of reflected (R) and transmitted (1-R) light:

$$R = \frac{1}{2}\frac{(a-c)^2}{(a+c)^2}\left\{1+\frac{[c(a+c)-1]^2}{[c(a-c)+1]^2}\right\}, \qquad (1)$$

where R is the Fresnel reflection of unpolarized light from air (refractive index = 1) to skin, where $c = \cos(\vartheta_i)$, ϑ_i is the angle of incidence, $a = n^2 + c^2 - 1$, and n is the refractive index of skin.

Refraction occurs as light passes from air to skin, or between regions of the skin whose refractive indices differ. Simulations

of skin optics which account for the effects of refraction generally do so through the application of Snell's law:

$$\theta_t = \arcsin\left(\frac{1}{n}\sin\,\theta_i\right), \tag{2}$$

where ϑ_t is the angle of refraction at the skin's surface.

Both Fresnel's equation and Snell's law require knowledge of the refractive indices of skin and the incident angle of light. Angles of incidence and transmission may be calculated simply for a skin model consisting smooth or flat interfaces. Refractive indices are generally obtained from direct measurements.[10]

5 Light Transport through Skin

The behavior of the remaining (transmitted) light is commonly simulated using radiative transfer theory (RTT).[28] This considers the transport of light in straight lines (beams). Absorption is modeled as a reduction in the radiance of a beam and is dependent upon the absorption coefficient (μ_a). The degree of scattering is described by both the scattering coefficient (μ_s), which considers both a loss of radiance in the direction of the beam and a gain from beams in other directions, and the phase function (p), which describes the distribution of scattering angles.

Due to the complex nature of skin, a general solution to the application of RTT is not available.[29] Thus, a further approximation is required. There are two main approaches to approximating the application of RTT; those which use a deterministic approach, and those which employ a stochastic 'ray tracing' technique. In addition, Prahl described an 'adding-doubling' method in his PhD thesis and associated publications.[28,30,31] This is a one dimensional iterative technique that uses RTT to estimate the transport of light through skin from the reflection and transmission of two or more mathematical 'slabs'. Although relatively simple in principle, it has not been used greatly outside of Prahl's work.

5.1 *Beer-Lambert Law*

The Beer-Lambert law is a simple deterministic technique which has been applied to estimate the reflectance (R) from a skin model. Although empirically derived,[32] this is essentially a solution to the application of RTT to the interaction of light with a static homogeneous absorbing (nonscattering) medium.

The Beer-Lambert law uses an estimate of the attenuation of light (A) obtained by measurements of on-axis transmission through thin samples of skin, and the optical path length (l):

$$R = e^{-Al}. \tag{3}$$

Modified versions of the Beer-Lambert law have been applied to estimate the quantities of melanin and hemoglobin in the skin.[33–35] These generally involve an additional exponential term to describe loss due to scattering and use an approximation of the mean optical path length $\langle l\rangle$, for example:

$$R_{\text{modified}} = e^{-\mu_a\langle l\rangle + A_0}, \tag{4}$$

where μ_a is the absorption coefficient, and A_0 is the attenuation caused by scatter. This technique is only applicable in a medium where absorption and scattering are relatively homogeneous.[35] In skin, where areas of high scattering (e.g., deep epidermis) and high absorption (such as those found in PWS skin) exist, the Beer-Lambert Law is not appropriate. Furthermore, it is not possible to account for the effects of vascular architecture in PWS skin using this method alone. When compared to an alternative simulation method, Shimada et al.[34] confirmed that the Beer-Lambert law is not sufficiently accurate for investigating human skin.

5.2 *Diffusion Approximation*

The diffusion approximation to RTT is by far the most widely used deterministic approach in biomedical optics, with Farrell et al.'s method[36] accumulating over 500 citations alone.[37]

The diffusion approximation is described in detail elsewhere.[28,38] In summary, it has a low demand for computing power and thus provides fast convergence for a wide range of applications. For example, it has been applied successfully to real-time light dosimetry during photodynamic therapy (PDT) of superficial skin cancers,[39,40] differentiation between pigmented skin lesions (including malignant melanoma),[41] and to determine blood oxygen saturation levels faster, and over a larger area than existing methods with equivalent reliability.[42] However, it suffers from a number of limitations, in part because it relies upon approximate solutions to an equation that itself represents an approximation to the equation of RTT.[43] For example, there is a requirement that scattering is dominant over absorption. This may be appropriate in clinically normal pale skin types, as the probability of scattering within the skin may be as high as twenty times that of absorption.[10,44] However, absorption is much greater in the epidermis of darker skin types, the blood vessel plexi of the normal dermis, and within PWS lesions. Thus, the validity of this approximation is limited in such cases.[34,43,45–47]

These drawbacks have limited the application of the diffusion approximation to investigations of PWS skin. For example, Verkruysse et al.[45] reported that data obtained from their two-layered skin model could be obtained quickly but compared poorly to measured spectra, resulting in an overestimation of blood volume fraction, oxygenation levels and melanin concentration in port wine stain (PWS) skin. Zhang et al.[48] found similar problems when applying a genetic algorithm minimization procedure to their diffusion approximation results, as did Lakmaker et al.[49] when investigating a method of predicting the maximal treatment depth response required for complete clearance of PWS lesions. Svaasand et al.[50] applied a diffusion approximation to their model, predicting the effects on skin color resulting from changes in the depth and thickness of a PWS lesion. However, simulated spectral reflectance curves compared poorly to their single example of a measured dataset, suggesting that these predictions of skin color may not be applicable on an individual basis.

5.3 *Monte Carlo Method*

Monte Carlo simulations used in biomedical optics are simply ray-tracing procedures, where a statistical analysis is used to calculate, step-by-step, the movements of simulated photons or light beams through a mathematical skin model[51] (see Fig. 3). This has been described as a discrete version of the radiative transport equation.[52] The Monte Carlo method was first introduced to the field of skin optics by Wilson and Adam in 1983[53] and was developed further by a number of groups over the next decade.[54–58] Although its use at this time was limited due to high demands in computing power, Monte Carlo methods are widely regarded as the most accurate simulations of light

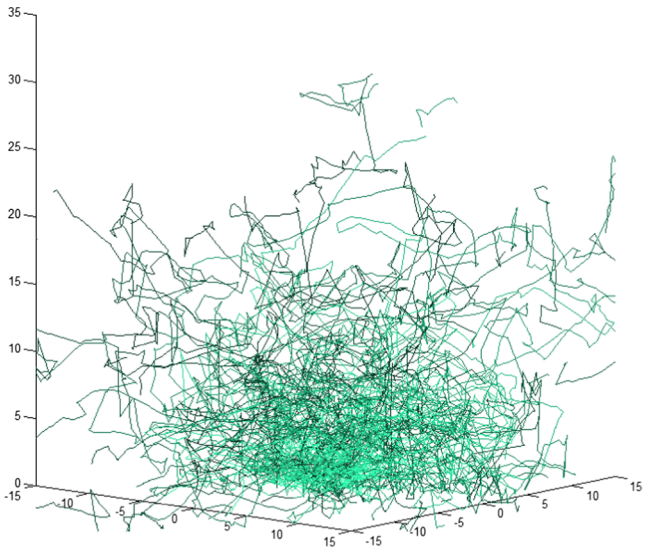

Fig. 3 Example of ray traces from 100 beams at a wavelength of 590 nm, simulated using a Monte Carlo program developed by the first author (T. Lister). Beams are initiated on the x-y plane (bottom of image). Reduction in beam 'weight' along each path is represented as a transition from light to dark green (color online). Dimensions in mm.

transport through skin,[48] and, as a result of recent advances in computing hardware, they are now routinely used for the interpretation of spectral data.[1]

In 1989, Keijzer et al. published their Monte Carlo simulation, analyzing the effectiveness of vascular laser treatments.[59] This program employs a two-layer skin model, and was developed for investigating PWS skin, in particular for determining the energy deposition within a single vessel during laser treatment. A pencil beam directed perpendicular to the surface of the skin model is initiated at a position randomly allocated within a circular region. The beam propagates through the skin model, undergoing absorption and scatter at events separated by a distance (s), calculated, as follows:

$$s = \frac{-\ln(\varepsilon)}{\mu_a + \mu_s}, \tag{5}$$

where ε is a random number generated from a uniform distribution between 0 and 1, μ_a is the absorption coefficient, and μ_s is the scattering coefficient. At the end of each 'step', a reduction in the beam weight (W, representing the total beam total energy of the beam) is calculated in accordance with Eq. (6):

$$\Delta W = W \frac{\mu_a}{\mu_a + \mu_s}. \tag{6}$$

Keijzer et al.'s program has the advantage of easy insertion of a sphere, ellipsoid or cylinder into the skin model, to simulate blood vessels for example, but lacks versatility as it uses a predetermined set of optical parameters determined from phantom measurements.

Keijzer et al.'s program was used by Lucassen et al.[60] to study the effects of laser wavelength on the response of PWS skin to laser therapy. The simulation calculated the absorbed energy within a single straight blood vessel of varying diameters, a curved blood vessel and multiple straight blood vessels. A 585-nm laser beam was predicted to be more effective than a 577-nm beam. This is in agreement with the results found in clinical practice, as a transition of standard practice between these two wavelengths followed worldwide (prior to the shift from 585 to 595 nm), as did the introduction of epidermal cooling during laser therapy, also recommended in Lucassen et al.'s study. Verkruysse et al.[61] also used Keijzer et al.'s simulation to study the influence of PWS anatomy on skin color. They created five models consisting of varying blood layers containing homogenous distributions of blood, with a correction factor to account for reduced light absorption when blood is contained within vessels. Verkruysse et al. commented that their simple skin model failed to take into account the effects of high epidermal scattering, even though they were able to model a diffuse irradiance of photons. Predicted changes of skin color with the removal of superficial vessels did not correspond with the reported clinical response.

In 1992, Wang and Jacques (the latter of which was listed as an author on the previously discussed paper by Keizer et al.) published a Monte Carlo simulation of steady-state light transport in multi-layered tissue using the ANSI Standard C computing language.[55,62] This program is freely available on the internet,[55] and allows users to create a two-dimensional skin model by inputting custom values of absorption coefficients, scattering coefficients, refractive indices and (Henyey-Greenstein) anisotropy factors for any number of layers. Like the program produced by Keijzer et al., the simulation begins with an infinitely narrow beam incident normal to the skin surface whose path through the skin is governed by Eqs. (5) and (6). A convolution algorithm may then be applied retrospectively to simulate a light source of finite size, such as a laser beam. This effectively repeats the results from the infinitely narrow beam over a finite area without performing any further simulations.

Mantis and Zonios[63] developed a two-layer mathematical skin model to estimate the thickness and absorption coefficient of a superficial absorbing layer using Wang and Jacques' Monte Carlo program. They inputted reflectance values obtained from a fiber optic spectrophotometer setup and compared them to the results simulated from an infinitesimally narrow incident laser beam. Nishidate et al.[64] applied the same program to a skin model consisting of an epidermis, dermis and local blood region. The depth and thickness of the simulated local blood region was adjusted until the simulated reflectance was in adequate agreement with a measured spectrum, forming an estimate of these parameters in the measured sample. They inputted measurements from a tissue phantom using a diffuse illuminant and a charge coupled device camera setup. Both studies reported absorption and reduced scattering coefficients with errors of around 10% compared to values expected from their skin phantoms. Considering the addition of uncertainty and optical inhomogeneity in a genuine skin sample, these errors are considerable. In fact, the study by Nishidate et al.[64] used the same method to estimate the depth of *in vivo* human veins. They reported errors of up to 0.6 mm for the depth and 0.2 mm for the thickness of veins when compared to ultrasound measurements. Again, these errors are large when considering normal skin thickness.[65]

Other research groups have developed Monte Carlo simulations for use in biomedical optics. Graaf et al. produced a condensed Monte Carlo simulation based upon the same governing equations [Eqs. (5) and (6)], but utilizing the derived relationship between simulated reflectance and albedo. In detail, the same simulated diffuse reflectance may be obtained by increasing the scattering coefficient and simultaneously decreasing

Table 1 Results from a simulation of 1 million photons. Values are presented for a simulation carried out using the Wang and Jacques Monte Carlo program (MCML)[62] with a simple, single-layered skin model of 1×10^8 cm depth; values of $g = 0.9$, refractive index = 1.3, and pencil beam irradiation used throughout (simulated by the first author, T. Lister).

Absorption coefficient (cm^{-1})	Scattering coefficient (cm^{-1})	Albedo	Calculated diffuse reflectance (MCML) (%)
1.0	50	0.980	18.4
1.0	100	0.990	28.7
0.5	50	0.990	28.7

the absorption coefficient, maintaining a fixed value of albedo (a dimensionless coefficient defined as the ratio of scattering coefficient to the sum of absorption and scattering coefficients).[66] To demonstrate the effects of varying absorption and scattering coefficients whilst maintaining a fixed albedo, we applied the following parameters to a simulation of 1 million photon packets, carried out using Wang and Jacques' program.[55] The skin model consisted of a single layer with an effectively infinite depth (1×10^8 cm) (Table 1).

This technique vastly improved simulation time for a uniform skin model and was shown to determine skin optical coefficients consistent with other studies.[10,67] This work was later extended by Wang et al.[68] who considered the effects of varying the diameter of the source. Wang et al. also demonstrated superior calculation times whilst maintaining good agreement with a standard Monte Carlo simulation.

Meglinski and Matcher's program[47,69] involved a seven layered skin model to simulate the reflectance spectrum of human skin, as measured using a fiber optic probe setup. Path lengths were calculated according to Eq. (7), and absorption coefficients were applied separately [Eq. (8)]:

$$s = \frac{-\ln(\varepsilon)}{\mu_s} \tag{7}$$

$$\Delta W = We^{-\mu_a s}. \tag{8}$$

The program has undergone a number of developmental steps since its first publication in 2001, and is currently available online as an interactive object oriented program with a multitude of potential outputs.[70,71]

Meglinski and Matcher found good agreement between their calculated reflectance and a single example of measured reflectance between 450 and 600 nm wavelengths, although the skin properties used outside of this wavelength range did not appear to provide a good agreement. This shortcoming may have been as a result of the constant scattering properties applied to the skin model over the entire wavelength range investigated. When applying the coefficients used by Meglinski and Matcher to Wang and Jacques' Monte Carlo program, Maeda et al.[72] reported a "rather strange spectral curve that had much worse agreement with measured results than (another set of coefficients)," demonstrating a clear discrepancy between the two programs.

In summary, Monte Carlo simulations have contributed substantially to the field of skin optics since their introduction in 1983.[53] Initial development by Keijzer et al.[59] and later by Wang and Jacques[55] facilitated a number of studies into the color of PWS skin. More recent work has demonstrated gradual development in Monte Carlo techniques for the simulation of PWS skin color and with continuing advancements in computing power available to the researcher, and an ever increasing interest in skin optics, such advances are likely to continue into the foreseeable future.

6 Conclusions

The color of PWS skin depends primarily upon the number, depth, and sizes of affected vessels. Thus, by measuring skin color, it may be possible to inform a better knowledge of these characteristics for an individual lesion, providing essential information for the optimization of laser treatment. The most common approach to extracting information from a measurement of skin color is through the inverse application of a skin model, whereby a simulation of light transport based upon RTT is performed.

Due to its low demand for computing power, the diffusion approximation has been applied widely in the field of skin optics. However, its limitations, along with the availability of increased computing power, have resulted in an increase in popularity of Monte Carlo simulations. Keijzer et al.'s and Wang and Jacques' Monte Carlo programs employed implicit capture to increase the speed of their simulations. These simulations have contributed significantly to the field of biomedical optics. However, recent developments have improved upon these, to provide faster and more accurate simulations of light transport through skin. As the scope for applying such techniques continues to broaden, with the possibility of introducing such a technique into routine clinical practice and with the continuing increase in computing power available to the researcher, further developments should be investigated to overcome the shortcomings of the studies presented here.

References

1. T. S. Lister, P. A. Wright, and P. H. Chappell, "Spectrophotometers for the clinical assessment of port wine stain skin lesions: a review," *Lasers Med. Sci.* **25**(3), 449 (2010).
2. R. G. Geronemus and R. Ashinoff, "The medical necessity of evaluation and treatment of port-wine stains," *J. Dermatologic Surg. Oncol.* **17**(1), 76–79 (1991).
3. A. Klein et al., "Laser and IPL treatment of port-wine stains: therapy options, limitations, and practical aspects," *Lasers Med. Sci.* **26**(6), 845–859 (2011).
4. A. Troilius, B. Wrangsjo, and B. Ljunggren, "Patients with port-wine stains and their psychosocial reactions after photothermolytic treatment," *Dermatologic Surg.* **26**(3), 190–196 (2000).
5. Y. C. Huang et al., "Noninvasive blood flow imaging for real-time feedback during laser therapy of port wine stain birthmarks," *Lasers Surg. Med.* **40**(3), 167–173 (2008).
6. Z. F. Jasim and J. M. Handley, "Treatment of pulsed dye laser-resistant port wine stain birthmarks," *J. Am. Acad. Dermatol.* **57**(4), 677–682 (2007).
7. K. V. T. Le, H. Shahidullah, and I. J. Frieden, "Review of modern techniques in detecting port-wine stain response to laser therapy," *Dermatol. Surg.* **25**(2), 127–132 (1999).
8. J. S. Nelson et al., "Infra-red tomography of port-wine-stain blood vessels in human skin," *Lasers Med. Sci.* **11**(3), 199–204 (1996).
9. M. J. C. van Gemert et al., "Non-invasive determination of port wine stain anatomy and physiology for optimal laser treatment strategies," *Phys. Med. Biol.* **42**(5), 937–950 (1997).

10. T. S. Lister, P. A. Wright, and P. H. Chappell, "The optical properties of human skin," *J. Biomed. Opt.* **17**(9), 090901 (2012).
11. P. Bjerring and P. H. Andersen, "Skin reflectance spectrophotometry," *Photodermatology* **4**(3), 167–171 (1987).
12. C. van der Horst et al., "Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed dye-laser," *New England J. Med.* **338**(15), 1028–1033 (1998).
13. D. C. Widdowson et al., "Construction of a novel port wine stain phantom and measurement of colour by digital imaging and reflectance spectrophotometry," *Lasers Med. Sci.* **23**(4), 369–374 (2008).
14. A. L. Fullerton et al., "Interlaboratory comparison and validity study of the Minolta ChromaMeters CR-200 and CR-300," *Skin Res. Technol.* **2**(3), 126–135 (1996).
15. E. Van den Kerckhove et al., "Reproducibility of repeated measurements on healthy skin with Minolta Chromameter CR-300," *Skin Res. Technol.* **7**(1), 56–59 (2001).
16. M. Huikeshoven et al., "Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment," *New England J. Medicine* **356**(12), 1235–1240 (2007).
17. R. R. Anderson and J. A. Parrish, "The optics of human skin," *J. Investigative Dermatol.* **77**(1), 13–19 (1981).
18. H. Takiwaki, "Measurement of skin color: practical application and theoretical considerations," *J. Med. Investigat.* **44**(3–4), 103–108 (1998).
19. S. H. Barsky et al., "Nature and evolution of port wine stains—computer-assisted study," *J. Investigative Dermatol.* **74**(3), 154–157 (1980).
20. E. J. Fiskerstrand, M. Dalaker, and L. T. Norvang, "Laser treatment of port-wine stains—a study comparing therapeutic outcome with morphologic characteristics of the lesions—preliminary-results," *Acta Dermato-Venereologica* **75**(1), 92–93 (1995).
21. E. J. Fiskerstrand et al., "Laser treatment of port wine stains: therapeutic outcome in relation to morphological parameters," *British J. Dermatol.* **134**(6), 1039–1043 (1996).
22. I. Nishidate, Y. Aizu, and H. Mishina, "Estimation of bluish appearance of veins in skin tissue using spectrocolorimetry," *Opt. Rev.* **9**(6), 269–276 (2002).
23. K. Yoshida et al., "Relationship between microstructure of the skin surface and surface reflection based on geometric optics," *J. Dermatol. Sci.* **66**(3), 225–232 (2012).
24. O. G. Cula et al., "Skin texture modeling," *Int. J. Comput. Vis.* **62**(1), 97–119 (2005).
25. G. V. G. Baranoski et al., "Increasing the predictability of tissue subsurface scattering simulations," *Vis. Comput.* **21**(4), 265–278 (2005).
26. E. Godfain, "Optical simulations of skin diagnosis with account of multiple surface scattering events," *Proc. SPIE* **3749**, 627–628 (1999).
27. M. Haedersdal et al., "Changes in skin redness, pigmentation, echostructure, thickness, and surface contour after 1 pulsed dye laser treatment of port-wine stains in children," *Arch. Dermatol.* **134**(2), 175–181 (1998).
28. A. J. Welch and M. J. C. van Gemert, Eds., *Optical-Thermal Response of Laser-Irradiated Tissue*, Plenum Publishing Corporation, New York (1995).
29. M. J. C. van Gemert et al., "Skin optics," *IEEE Trans. Biomed. Eng.* **36**(12), 1146–1154 (1989).
30. S. A. Prahl, "Light transport in tissue," Ph.D. Thesis, p. 160 The University of Texas at Austin, Austin, Texas (1988).
31. S. A. Prahl, "Optical property measurements using the inverse adding-doubling program," in *Optical-Thermal Response of Laser Irradiated Tissue*, A. J. Welch and M. J. C. van Gemert, Eds., pp. 101–129, Plenum Publishing Corporation, New York (1995).
32. P. Bouguer, "*Essai d'optique sur la gradation de la lumiere*," Claude Jombert, Paris (1729).
33. P. H. Andersen and P. Bjerring, "Noninvasive computerized analysis of skin chromophores *in vivo* by reflectance spectroscopy," *Photodermatol. Photoimmunol. Photomed.* **7**(6), 249–257 (1990).
34. M. Shimada et al., "Melanin and blood concentration in a human skin model studied by multiple regression analysis: assessment by Monte Carlo simulation," *Phys.Med. Biol.* **46**(9), 2397–2406 (2001).
35. A. A. Stratonnikov et al., "Application of backward diffuse reflection spectroscopy for monitoring the state of tissues in photodynamic therapy," *Quantum Electron.* **36**(12), 1103–1110 (2006).
36. T. J. Farrell, M. S. Patterson, and B. Wilson, "A diffusion-theory model of spatially resolved, steady-state diffuse reflectance for the noninvasive determination of tissue optical-properties *in-vivo*," *Med. Phys.* **19**(4), 879–888 (1992).
37. Anon Institute for Scientific Information, "Web of Knowledge (WoK)," http://isiknowledge.com/ (27 January 2012).
38. W. F. Cheong, S. A. Prahl, and A. J. Welch, "A review of the optical-properties of biological tissues," *IEEE J. Quantum Electron.* **26**(12), 2166–2185 (1990).
39. D. L. Glennie et al., "integrating spheres for improved skin photodynamic therapy," *J. Biomed. Opt.* **15**(5), 058001 (2010).
40. A. Amelink et al., "Monitoring PDT by means of superficial reflectance spectroscopy," *J. Photochem. Photobiol. B-Biol.* **79**(3), 243–251 (2005).
41. V. P. Wallace et al., "Spectrophotometric assessment of pigmented skin lesions: methods and feature selection for evaluation of diagnostic performance," *Phys. Med. Biol.* **45**(3), 735–751 (2000).
42. S. Gioux et al., "Preclinical and clinical validation of a novel oxygenation imaging system," *Proc. SPIE* **7896**, 78961R (2011).
43. V. Venugopalan, J. S. You, and B. J. Tromberg, "Radiative transport in the diffusion approximation: an extension for highly absorbing media and small source-detector separations," *Phys. Rev. E* **58**(2), 2395–2407 (1998).
44. G. Ackermann et al., "Correlations between light penetration into skin and the therapeutic outcome following laser therapy of port-wine stains," *Lasers Med. Sci.* **17**(2), 70–78 (2002).
45. W. Verkruysse et al., "A library based fitting method for visual reflectance spectroscopy of human skin," *Phys. Med. Biol.* **50**(1), 57–70 (2005).
46. T. J. Pfefer et al., "Modeling laser treatment of port wine stains with a computer-reconstructed biopsy," *Lasers Surg. Med.* **24**(2), 151–166 (1999).
47. I. V. Meglinski and S. J. Matcher, "Computer simulation of the skin reflectance spectra," *Comput. Meth. Programs Biomed.* **70**(2), 179–186 (2003).
48. R. Zhang et al., "Determination of human skin optical properties from spectrophotometric measurements based on optimization by genetic algorithms," *J. Biomed. Opt.* **10**(2), 024030 (2005).
49. O. Lakmaker, J. W. Pickering, and M. J. C. van Gemert, "Modeling the color-perception of port wine stains and its relation to the depth of laser coagulated blood-vessels," *Lasers Surg. Med.* **13**(2), 219–226 (1993).
50. L. O. Svaasand et al., "Tissue parameters determining the visual appearance of normal skin and port-wine stains," *Lasers Med. Sci.* **10**(1), 55–65 (1995).
51. A. Kienle and R. Hibst, "A new optimal wavelength for treatment of port-wine stains," *Phys. Med. Biol.* **40**(10), 1559–1576 (1995).
52. P. Y. Liu, "A new phase function approximating to mie scattering for radiative transport-equations," *Phys. Med. Biol.* **39**(6), 1025–1036 (1994).
53. B. C. Wilson and G. Adam, "A Monte-Carlo model for the absorption and flux distributions of light in tissue," *Med. Phys.* **10**(6), 824–830 (1983).
54. S. A. Prahl et al., "A Monte Carlo model of light propagation in tissue," *SPIE Proc. Dosimetry Laser Radiation Med. Biol.* **IS 5**, 102–111 (1989).
55. L. Wang and S. L. Jacques, *Monte Carlo Modeling of Light Transport in Multi-Layered Tissues in Standard C*, Anderson Cancer Centre, University of Texas, Houston (1992).
56. S. T. Flock et al., "Monte-Carlo modeling of light-propagation in highly scattering tissues 1. Model predictions and comparison with diffusion-theory," *IEEE Trans. Biomed. Eng.* **36**(12), 1162–1168 (1989).
57. S. T. Flock, B. C. Wilson, and M. S. Patterson, "Monte-Carlo modeling of light-propagation in highly scattering tissues. 2. Comparison with measurements in phantoms," *IEEE Trans. Biomed. Eng.* **36**(12), 1169–1173 (1989).
58. M. Keijzer et al., "Light distributions in artery tissue—Monte-Carlo simulations for finite-diameter laser-beams," *Lasers Surg. Med.* **9**(2), 148–154 (1989).
59. M. Keijzer, "Light transport for medical laser treatments," Ph.D. Thesis, Technische University, Delft, The Netherlands (1993).
60. G. W. Lucassen et al., "Light distributions in a port wine stain model containing multiple cylindrical and curved blood vessels," *Lasers Surg. Med.* **18**(4), 345–357 (1996).

61. W. Verkruysse, G. W. Lucassen, and M. J. C. van Gemert, "Simulation of color of port wine stain skin and its dependence on skin variables," *Lasers in Surg. Med.* **25**(2), 131–139 (1999).
62. L. Wang, S. L. Jacques, and L. Zheng, "MCML—Monte Carlo modeling of light transport in multi-layered tissues," *Comput. Meth. Programs Biomed.* **47**(2), 131–146 (1995).
63. G. Mantis and G. Zonios, "Simple two-layer reflectance model for biological tissue applications," *Appl. Opt.* **48**(18), 3490–3496 (2009).
64. I. Nishidate et al., "Visualizing depth and thickness of a local blood region in skin tissue using diffuse reflectance images," *J. Biomed. Opt.* **12**(5), 054006 (2007).
65. P. Krackowizer and E. Brenner, "Thickness of the human skin: 24 points of measurement," *Phlebol.* **37**(2), 83–92 (2008).
66. R. Graaff et al., "Condensed Monte Carlo simulations for the description of light transport," *Appl. Opt.* **32**(4), 426–434 (1993).
67. R. Graaff et al., "Optical properties of human dermis *in vitro* and *in vivo*," *Appl. Opt.* **32**(4), 435–447 (1993).
68. Q. Wang et al., "Condensed Monte Carlo modeling of reflectance from biological tissue with a single illumination detection fiber," *IEEE J. Select. Topics Quantum Electron.* **16**(3), 627–634 (2010).
69. I. V. Meglinski and S. J. Matcher, "Quantitative assessment of skin layers absorption and skin reflectance spectra simulation in the visible and near-infrared spectral regions," *Physiol. Meas.* **23**(4), 741–753 (2002).
70. A. Doronin and I. Meglinski, "Online object oriented Monte Carlo computational tool for the needs of biomedical optics," *Biomed. Opt. Express* **2**(9), 2461–2469 (2012).
71. I. Meglinski and A. Doronin, "MC Online," http://biophotonics.otago.ac.nz/MCOnline.aspx (5 October 2012).
72. T. Maeda et al., "Monte Carlo simulation of spectral reflectance using a multilayered skin tissue model," *Opt. Rev.* **17**(3), 223–229 (2010).