2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

On the Sensitivity of Skin Spectral Responses to Variations in the Thickness of the Cutaneous Tissues

Gladimir V. G. Baranoski[1], Spencer R. Van Leeuwen[1] and Francis T. Chen[1]

***Abstract*— A wide range of devices are being routinely used in the noninvasive screening and monitoring of medical conditions through the analysis of skin spectral responses. The correct interpretation of these responses often depends on the availability of high-fidelity characterization datasets for the selected specimens. More specifically, the higher their fidelity, the more effective the quantification of changes observed in a given biophysical variable of interest. Skin thickness is among the most relevant of these parameters since it plays a pivotal role in the attenuation (scattering and absorption) of light traversing the cutaneous tissues. Transient and permanent physiological processes, such as tanning and ageing, can result in significant time-dependent thickness variations. These, in turn, can introduce biases in the comparison of skin spectral responses obtained at different time instances. In this paper, we investigate the impact of thickness variations on skin reflectance with respect to different regions of light spectrum. Our findings are expected to contribute to the mitigation of interpretation errors and, thus, to the enhancement of noninvasive screening and monitoring procedures based on skin spectral responses.**

***Index Terms*— reflectance, ageing, tanning, skin thinning, skin thickening, *in silico* experiments, noninvasive screening.**

I. Introduction

In the last decades, a diverse array of optical devices have been proposed to support the diagnosis and treatment of diseases [1], [2]. A considerable number of these devices are based on the noninvasive acquisition and interpretation of skin spectral responses, and aimed at the detection of specific medical conditions such as hyperbilirubinemia [3], anemia [4] and melanoma [5], [6], just to name a few. Variations in skin characterization parameters over time represent one of the main challenges in this area. These variations, which can result from physiological processes that may be unrelated to a given medical condition under investigation, can alter skin spectral responses. Consequently, they can hinder the screening and monitoring of this condition by masking changes in pivotal biophysical parameters (*e.g.*, the high concentration of bilirubin in the cutaneous tissues elicited by hyperbilirubinemia and leading to the onset of jaundice, the resulting yellow-tinted skin appearance [7]).

One of the key sets of parameters used in the characterization of a skin specimen corresponds to the thicknesses of its constituent tissues, notably for applications involving the interpretation of its spectral responses. Concisely speaking, these responses can be quantified in terms of how much light is reflected by a specimen at specific wavelengths, which depends on the amount of light absorbed and scattered within its constituent tissues at these wavelengths. Since these attenuation events take place while light is traversing a tissue, their probability is tied to its path length inside this tissue. Thus, variations in the cutaneous tissues' thicknesses can affect the resulting skin spectral reflectance. These variations, thickening and/or thinning, may occur over time due to transient or permanent physiological processes such as tanning [8], [9] and ageing [10], [11], respectively. As a result, they may affect the comparison of skin spectral responses obtained at distinct time instances to determine biophysical changes associated with a specific medical condition.

Although, from a tissue optics point of view, variations in the thickness of the cutaneous tissues are likely to affect skin spectral responses, the quantification of their sensitivity to these variations remains largely unexplored, particularly with respect to different spectral regions, within the ultraviolet (UV), visible (Vis) and infrared (IR) domains. One of the main reasons can be attributed to the difficulties of performing controlled *in vitro* or *in vivo* experiments on a specimen over time. These difficulties involve, for instance, replicating the same measurement conditions from one experimental instance to another, and keeping the other biophysical parameters not under examination (*e.g.*, amount of blood in the dermis) fixed for the selected specimen over the duration of a given experiment.

In this paper, we present a detailed assessment of the sensitivity of skin spectral responses to variations in the thickness of cutaneous tissues elicited by physiological processes like tanning and ageing. To overcome the aforementioned experimental constraints, we employed an *in silico* (computational) investigation approach [12] supported by measured data provided in the related literature. Using this approach, we carried out controlled experiments to examine the wavelength-dependent impact of cutaneous thickness variations on the reflectance of representative skin specimens characterized by distinct pigmentation levels. It is worth noting that certain spectral regions are more relevant than others for specific noninvasive medical applications. For example, while ultraviolet is particularly relevant for the assessment of skin cancer [13], the visible and infrared domains are often considered in the assessment of conditions such as such as hyperbilirubinemia [3], [14], anemia [4] and dehydration [15]. For this reason, in this investigation, we performed a piecewise sensitivity analysis of the impact of thickness variations on skin reflectance with respect to distinct regions of the light spectrum from 280 to 2500 nm.

*This work was supported in part by the Natural Sciences and Research Council of Canada (NSERC) under Grant 238337.

[1] The authors are with the Natural Phenomena Simulation Group, School of Computer Science, University of Waterloo, 200 University Avenue, Waterloo, Ontario, N2L 3G1, Canada. gvgbaran@cs.uwaterloo.ca

II. In Silico Experimental Framework

In this work, we used a first-principles model of light and skin interactions, known as HyLIoS (*H*yperspectral *L*ight *I*mpingement on *S*kin) [16], to compute directional-hemispherical reflectance curves for typical specimens, henceforth referred to as lightly pigmented (LP) and darkly pigmented (DP). We note that the radiometric predictions provided by this model have been extensively evaluated through comparisons of its outcomes with actual measured data [16], and effectively employed in a wide range of biomedical investigations (*e.g.*, [17], [18], [19], [20], [21]).

The parameters used to characterize the LP and DP specimens considered in this investigation are provided in Table I and Table II. The selection of values for these parameters was based on their respective physiologically ranges provided in the related literature. These sources, unless otherwise cited below, are listed elsewhere [19] for conciseness. Using these datasets, we computed the control reflectance curves for both specimens as well as reflectance curves associated with variations in the thickness of their main cutaneous tissues (stratum corneum, stratum granulosum, stratum spinosum, stratum basale, papillary dermis and reticular dermis) on the order of $\pm 25\%$. We selected this variation range and uniformly applied it to the tissues' thickness taking into account data (obtained at distinct anatomical (body) locations) also provided in the related literature [9], [10], [11], [20].

TABLE I

HyLIoS parameters employed in the specific characterization of the LP (lightly pigmented) and DP (darkly pigmented) skin specimens considered in this investigation. The acronyms SC, SG, SS, SB, PD and RD refer to their main tissues: stratum corneum, stratum granulosum, stratum spinosum, stratum basale, papillary dermis and reticular dermis, respectively.

Parameter	Value (LP)	Value (DP)
SC Thickness (cm)	0.001	0.002
SG Thickness (cm)	0.0011	0.0015
SS Thickness (cm)	0.0011	0.0015
SB Thickness (cm)	0.0011	0.0015
PD Thickness (cm)	0.04	0.023
RD Thickness (cm)	0.1	0.2
SC Melanosome Content (%)	0.0	0.0
SG Melanosome Content (%)	0.8	5.0
SS Melanosome Content (%)	0.8	5.0
SB Melanosome Content (%)	0.8	5.0
PD Melanosome Content (%)	0.0	0.0
RD Melanosome Content (%)	0.0	0.0
SC Colloidal Melanin Content (%)	0.0	0.0
SG Colloidal Melanin Content (%)	3.9	5.0
SS Colloidal Melanin Content (%)	3.9	5.0
SB Colloidal Melanin Content (%)	3.9	5.0
PD Colloidal Melanin Content (%)	0.0	0.0
RD Colloidal Melanin Content (%)	0.0	0.0
Melanosome Dimensions ($\mu m \times \mu m$)	0.41×0.17	0.69×0.28
Melanosome Eumelanin Conc. (g/L)	50.0	50.0
Melanosome Pheomelanin Conc. (g/L)	2.0	4.0
PD Blood Content (%)	0.2	0.5
RD Blood Content (%)	0.2	0.2
Dermal Oxyhemoglobin Fraction (%)	75.0	90.0
Hemoglobin Conc. in Blood (g/L)	130.0	147.0

Within the HyLIoS' geometrical-optics formulation, a ray interacting with a given skin specimen can be associated with any wavelength within a spectral region of interest. For consistency, we considered a spectral resolution of 5 nm in all reflectance curves presented in this work, which were computed using a virtual spectrophotometer [22]. In their computation, we considered two angles of incidence, namely 15° and 45°, to increase our scope of observations, and employed 10^6 sample rays (per sampled wavelength). To enable the full reproduction of our results, we made HyLIoS available online [23], [24] along with the supporting biophysical datasets (*e.g.*, refractive index and extinction coefficient curves) used in our *in silico* experiments.

TABLE II

HyLIoS parameters employed in the characterization of both skin specimens considered in this investigation. The acronyms SC, SG, SS, SB, PD and RD refer to their main tissues: stratum corneum, stratum granulosum, stratum spinosum, stratum basale, papillary dermis and reticular dermis, respectively.

Parameter	Value
Ratio of Skin Surface Folds	0.1
Methemoglobin Conc. in Blood (g/L)	1.5
Carboxyhemoglobin Conc. in Blood (g/L)	1.5
Sulfhemoglobin Conc. in Blood (g/L)	0.0
Bilirubin Conc. in Blood (g/L)	0.003
Extravascular Bilirubin Conc. (g/L)	0.0
Beta-Carotene Conc. (g/L)	2.1E-4
Epidermis Beta-Carotene Conc. (g/L)	2.1E-4
Blood Beta-Carotene Conc. (g/L)	7.0E-5
SC Water Content (%)	35.0
Epidermis Water Content (%)	60.0
PD Water Content (%)	75.0
RD Water Content (%)	75.0
SC Lipid Content (%)	20.0
Epidermis Lipid Content (%)	15.1
PD Lipid Content (%)	17.33
RD Lipid Content (%)	17.33
SC Keratin Content (%)	65.0
SC Urocanic Acid Density (mol/L)	0.01
Skin DNA Density (g/L)	0.185
Melanin Refractive Index	1.7
SC Refractive Index	1.55
Epidermis Refractive Index	1.4
PD Refractive Index	1.39
RD Refractive Index	1.41
Melanin Refractive Index	1.7
PD Scatterers Refractive Index	1.5
Radius of PD Scatterers (nm)	70.0
PD Fraction Occupied by Scatterers (%)	22.0

In order to examine spectrally-dependent patterns resulting from our *in silico* experiments more systematically, we performed a differential sensitivity analysis [25], [26] on the modeled reflectance curves across nine spectral regions: UVB (280 to 315 nm), UVA (315 to 380 nm), Vis-B (380 to 485 nm), Vis-G (485 to 590 nm), Vis-R (590 to 700 nm), IRA-1 (700 to 1050 nm), IRA-2 (1050 to 1400 nm), IRB-1 (1400 to 2050 nm) and IRB-2 (2050 to 2500 nm). This analysis involved the computation of a sensitivity index (SI) that provides the ratio of the change in output to the change in a quantity of interest while the other input quantities are kept fixed [26]. A ratio equal to 1.0 indicates complete sensitivity (or maximum impact), while a ratio less than 0.01 indicates that the measured/modeled

quantity is insensitive to changes in the selected input quantity [18], [27]. Accordingly, we computed the mean sensitivity index (MSI) for the spectral regions of interest to assess the mean ratio of change in reflectance with respect to the skin thickness variations. This index is expressed as:

$$MSI = \frac{1}{N}\sum_{i=1}^{N} SI_i = \frac{1}{N}\sum_{i=1}^{N} \frac{|\rho_c(\lambda_i) - \rho_t(\lambda_i)|}{\max\{\rho_c(\lambda_i), \rho_t(\lambda_i)\}}, \quad (1)$$

where ρ_c and ρ_t correspond to the reflectances associated with the control and thickness-altered cases, respectively, computed for a given skin specimen, and N is the total number of wavelengths sampled with a 5 nm resolution within a selected spectral region.

III. Results and Discussion

As shown in the graphs presented in Fig. 1, the reduction of the cutaneous tissues' thickness resulted in a noticeable increase in the specimens' reflectance in several spectral regions. Conversely, the thickness increase resulted in a noticeable reflectance decrease in these regions. These qualitative trends were observed for both angles of incidence considered in this investigation as it can be verified by comparing the graphs presented in Fig. 1 with those presented in Fig. 2.

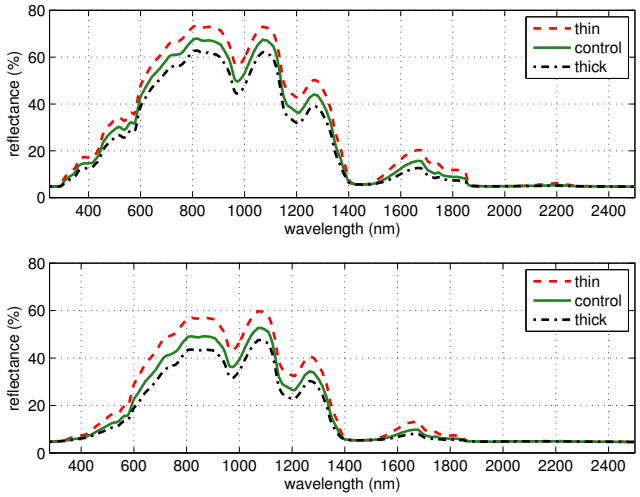

Fig. 1. Graphs depicting the sets of spectral reflectance curves obtained for the selected specimens considering an angle of incidence of 15°. Top: lightly pigmented (LP) specimen. Bottom: darkly pigmented (DP) specimen. The curves correspond to the distinct values assigned to thickness of their cutaneous tissues: control (default values provided in Table I), thin (25% lower values) and thick (25% higher values).

Upon a closer visual inspection of the reflectance curves presented in Figs. 1 and 2, one can observe that the magnitudes of the reflectance increases are slightly larger than that of the decreases. These differences may be attributed to the fact that the light attenuation processes within the cutaneous tissues are nonlinear [16]. In fact, these differences in the visible range are more noticeable for the DP specimen than for the LP specimen.

We remark that, in this work, we are focusing on the qualitative effects of thickness variations. Accordingly, these effects are examined in a controlled manner, *i.e.*, other

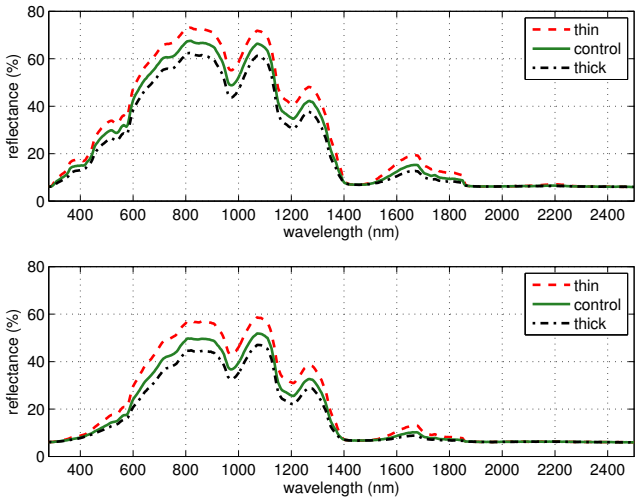

Fig. 2. Graphs depicting the sets of spectral reflectance curves obtained for the selected specimens considering an angle of incidence of 45°. Top: lightly pigmented (LP) specimen. Bottom: darkly pigmented (DP) specimen. The curves correspond to the distinct values assigned to thickness of their cutaneous tissues: control (default values provided in Table I), thin (25% lower values) and thick (25% higher values).

characterization parameters (*e.g.*, volume fraction (%) of the tissues occupied by a given pigment) are kept fixed. It is worth noting, however, certain particular biophysical correlations. For instance, a thickness increase (hyperplasia) following a tanning process is accompanied by an increase in melanin content within the epidermal tissues [20]. Since melanin dominates light absorption within the epidermal tissues in the ultraviolet and spectral domains [16], a larger amount of this pigment intensifies the reflectance reduction within these domains elicited by an increase in the thickness of the epidermal tissues. Similarly, during a dehydration process, tissue thinning (shrinkage) is accompanied by a water loss [28]. Since water dominates light absorption within the cutaneous tissues in the infrared domain [16], such a water content reduction intensifies the reflectance increase within this domain elicited by a skin thickness reduction.

The MSI values computed for the LP specimen, which are presented in Fig. 3, indicate a higher impact of thickness variations in its reflectance in the UVA and IRB-1 regions. These MSI values are slightly lower for the larger angle of incidence, which may be attributed to a higher probability of light reflection on the specimen's surface. Furthermore, these values are higher for the thickness reduction than for its increase, which, again, can be attributed to the nonlinearity of the light attenuation processes mentioned earlier.

The MSI values computed for the DP specimen, which are presented in Fig. 4, indicate a similar impact of thickness variations on its reflectance in the IRB-1 region. This was to be expected since we considered the same percentage of water (Table II) for both specimens. However, these MSI values also indicate a higher impact in the reflectance in the visible domain when compared with the values obtained by the LP specimen. These aspects can be explained by the higher percentage of melanin (Table I) used in the characterization of the DP specimen.

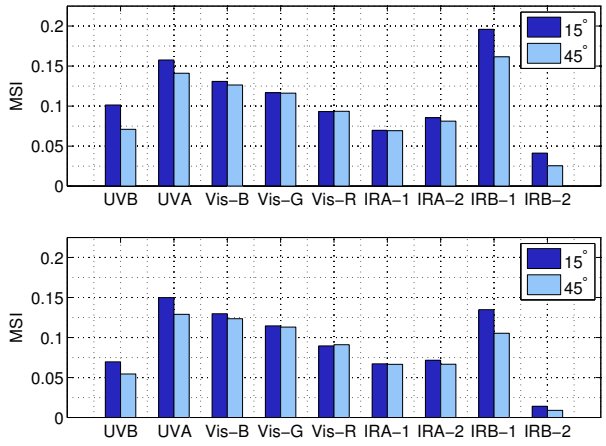

Fig. 3. Mean sensitivity index (MSI) values computed for the lightly pigmented (LP) specimen's reflectance curves obtained considering variations in the thickness of its cutaneous tissues and two angles of incidence: $15°$ and $45°$. Top: a 25% thickness reduction. Bottom: a 25% thickness increase.

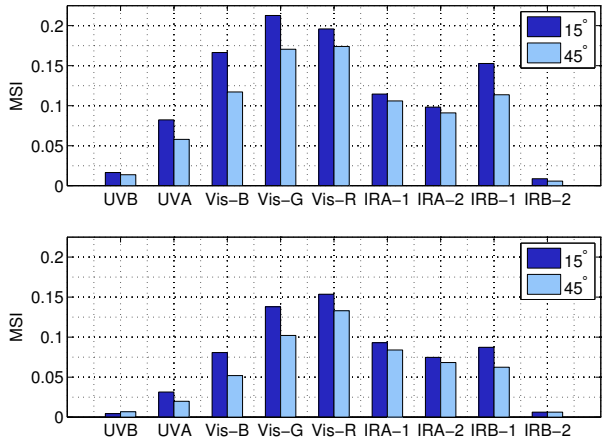

Fig. 4. Mean sensitivity index (MSI) values computed for the darkly pigmented (DP) specimen's spectral reflectance curves obtained considering variations in the thickness of its cutaneous tissues and two angles of incidence: $15°$ and $45°$. Top: a 25% thickness reduction. Bottom: a 25% thickness increase.

The MSI values depicted in Fig. 4 are also lower for the larger angle of incidence and thickness increase, except for values computed for the UVB and IRB-2 regions considering the thickness increase and the angle equal to $45°$. In these two cases, however, the MSI values were below 0.01. We remark that this indicates that the measured/modeled quantity (reflectance) is insensitive to changes in the selected specimen characterization parameter (thickness) [27]. Hence, for practical purposes, these exceptions are negligible.

For completeness, we also computed the maximum SI values within each spectral region of interest. These values are presented in Tables III and IV. While for the LP specimen, higher values were obtained within the ultraviolet and infrared domains, for the DP specimen, higher values were obtained in the visible and infrared domains. Overall, for both specimens and both angles of incidence, the highest values were associated with the skin thickness reduction and obtained in the IRB-1 region, around the bands of absorption minima of water. Furthermore, except for the LP specimen in the Vis-G region, the maximum SI values computed for the reflectance curves associated with the skin thickness reduction were equal or higher than those computed for the curves associated with the thickness increase. Again, this highlights the nonlinearity of effects of thickness variations.

There were noticeable quantitative differences between the maximum SI values computed for the reflectance curves obtained considering $15°$ (Table III) and $45°$ (Table IV), with the former being generally higher in most instances. However, the aforementioned qualitative observations were the same for both sets of maximum SI values.

TABLE III

MAXIMUM SENSITIVITY INDEX (SI) VALUES COMPUTED FOR THE LIGHTLY PIGMENTED (LP) AND DARKLY PIGMENTED (DP) SPECIMENS' REFLECTANCE CURVES OBTAINED CONSIDERING AN ANGLE OF INCIDENCE OF $15°$ AND $\pm 25\%$ VARIATIONS IN THEIR SKIN THICKNESS. THE SIS' CORRESPONDING WAVELENGTHS (λ) ARE PROVIDED IN nm.

	LP Specimen Thickness				DP Specimen Thickness			
Spectral	-25%		+25%		-25%		+25%	
Region	SI	λ	SI	λ	SI	λ	SI	λ
UVB	0.16	315	0.13	315	0.03	315	0.01	310
UVA	0.17	360	0.16	370	0.13	375	0.05	380
Vis-B	0.16	380	0.16	385	0.23	485	0.16	485
Vis-G	0.12	495	0.13	490	0.25	505	0.15	515
Vis-R	0.11	590	0.10	590	0.22	595	0.17	610
IRA-1	0.12	970	0.11	980	0.17	705	0.14	705
IRA-2	0.23	1380	0.17	1365	0.24	1365	0.18	1360
IRB-1	0.26	1810	0.20	1665	0.26	1670	0.18	1675
IRB-2	0.14	2190	0.05	2180	0.03	2205	0.02	2030

TABLE IV

MAXIMUM SENSITIVITY INDEX (SI) VALUES COMPUTED FOR THE LIGHTLY PIGMENTED (LP) AND DARKLY PIGMENTED (DP) SPECIMENS' REFLECTANCE CURVES OBTAINED CONSIDERING AN ANGLE OF INCIDENCE OF $45°$ AND $\pm 25\%$ VARIATIONS IN THEIR SKIN THICKNESS. THE SIS' CORRESPONDING WAVELENGTHS (λ) ARE PROVIDED IN nm.

	LP Specimen Thickness				DP Specimen Thickness			
Spectral	-25%		+25%		-25%		+25%	
Region	SI	λ	SI	λ	SI	λ	SI	λ
UVB	0.13	315	0.11	310	0.04	315	0.01	310
UVA	0.16	360	0.15	365	0.09	370	0.03	380
Vis-B	0.15	385	0.14	390	0.18	485	0.09	485
Vis-G	0.12	490	0.13	485	0.18	505	0.12	590
Vis-R	0.11	590	0.11	590	0.19	610	0.14	630
IRA-1	0.12	980	0.11	970	0.16	705	0.13	705
IRA-2	0.20	1385	0.15	1365	0.21	1360	0.15	1345
IRB-1	0.22	1745	0.17	1675	0.22	1680	0.14	1655
IRB-2	0.09	2195	0.03	2200	0.03	2205	0.02	2010

Our findings show that the impact of thickness variations on skin reflectance is not uniform across the light spectrum, and it can be significant (above 20%) in certain spectral regions depending on the specimen's biophysical charac-

teristics. Hence, they need to be appropriately accounted for during the analysis of skin spectral readings obtained at these regions, particularly when these measurements are performed at markedly distinct time instances. We note that the monitoring of long-term medical conditions may require a time interval between these measurements on the order of days or years. During this period, the patient may be subject to physiological processes, such as tanning or ageing, that are correlated with changes in skin thickness as outlined earlier. Such changes, in turn, can introduce errors in the interpretation of her/his skin spectral responses, which can increase the possibility of false positive or false negative evaluations of the medical condition under observation.

Finally, we remark that this research was aimed at assessing the overall sensitivity of skin reflectance to thickness variations. Thus, we have considered these variations uniformly occurring in all main cutaneous tissues. In our future investigations in this area, we intend to examine the impact that such variations can have on skin reflectance when they are nonuniformly applied to specific tissues [29], [30].

IV. Concluding Remarks

In this work, we have used an *in silico* experimental framework to assess the sensitivity of skin spectral responses to thickness variations. Such an approach is being extensively employed in health-related research, notably involving the noninvasive screening and monitoring of diseases. We believe, however, that it should not be seen as a replacement for traditional laboratory experiments, but rather as a dependable ally. In fact, our *in silico* investigation highlighted the importance of obtaining reliable specimen characterization data, such as skin thickness, through actual measurements. Accordingly, future efforts toward the acquisition of such data should be fomented by the biomedical community.

References

[1] V.V. Tuchin, *Tissue optics: light scattering methods and instruments for medical diagnosis*, SPIE PM. SPIE/International Society for Optical Engineering, Bellingham, WA, USA, 2007.

[2] F. Khatun, Y. Aizu, and I. Nishidate, "Monitoring of hemoglobin derivatives using a red-green-blue camera-based spectral imaging technique," *Int. J. Mol. Sci.*, vol. 22, pp. 1528:1–17, 2021.

[3] B.G. Harbrecht, M.R. Rosengart, K. Bukauskas, M.S. Zenati, J.W. Marsh Jr., and D.A. Geller, "Assessment of transcutaneous bilirubinometry in hospitalized adults," *J. Am. Coll. Surg.*, vol. 206, no. 6, pp. 1129–1136, 2008.

[4] A. Yoshida, K. Saito, K. Ishi, I. Azuma, H. Sasa, and K. Furuya, "Assessment of noninvasive, percutaneous hemoglobin measurement in pregnant and early postpartum women," *Med. Devices: Evid. Res.*, vol. 7, pp. 11–16, January 2014.

[5] J. Welzel and S. Schuh, "Noninvasive diagnosis in dermatology," *J. German Soc. Dermatol.*, vol. 15, no. 10, pp. 999–1016, 2017.

[6] G. Zonios, A. Dimou, I. Bassukas, D. Galaris, A. Tsolakidis, and E. Kaxiras, "Melanin absorption spectroscopy: new method for noninvasive skin investigation and melanoma detection," *J. Biomed. Optics*, vol. 13, no. 1, pp. 014017, 2008.

[7] G.V.G Baranoski, T.F. Chen, and P. Varsa, "On the effective differentiation and monitoring of variable degrees of hyperbilirubinemia severity through noninvasive screening protocols," in *40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Honolulu, HI, USA, July 2018, pp. 4981–4986.

[8] A.D. Pearse, S.A. Gaskell, and R. Marks, "Epidermal changes in human skin following irradiation with either UVB or UVA," *J. Invest. Dermatol.*, vol. 88, no. 1, pp. 83–87, 1987.

[9] H. Lopez, Z.J. Beer, S.A. Miller, and B.Z. Zmudzka, "Ultrasound measurements of skin thickness after UV exposure: a feasibility study," *J. of Photochem. Photobiol. B*, vol. 73, no. 3, pp. 123–132, 2004.

[10] C.Y. Tan, B. Strathum, R. Marks, and P.A. Payne, "Skin thickness measurement by pulsed ultrasound: its reproducibility, validation and variability," *Brit. J. Dermatol.*, vol. 106, no. 6, pp. 657–667, 1982.

[11] C. Lasagni and S. Seidenari, "Echographic assessment of age-dependent variations of skin thickness," *Skin Res. Technol.*, vol. 1, pp. 81–85, 1995.

[12] M. Viceconti, A. Henney, and E. Morley-Fletcher, "In silico clinical trials: how computer simulation will transform the biomedical industry," *Int. J. Clin. Trials*, vol. 3, no. 2, pp. 37–46, 2016.

[13] G.J. Clydesdale, G.W. Dandie, and H.K. Muller Konrad, "Ultraviolet light induced injury: immunological and inflammatory effects," *Immunol. Cell. Biol.*, vol. 79, no. 6, pp. 547– 568, 2001.

[14] S.N. El-Beshbishi, K.E. Shattuck, A.A. Mohammad, and J.R. Petersen, "Hyperbilirubinemia and transcutaneous bilirubinometry," *Clin. Chem.*, vol. 5, no. 7, pp. 1280–1287, 2009.

[15] M. Attas, T. Posthumus, B. Schattka, M. Sowa, H. Mantsch, and S. Zhang, "Long-wavelength near-infrared spectroscopic imaging for in-vivo sky hydration measurements," *Vib. Spectrosc.*, vol. 28, pp. 37–43, 2002.

[16] T.F. Chen, G.V.G. Baranoski, B.W. Kimmel, and E. Miranda, "Hyperspectral modeling of skin appearance," *ACM Trans. Graph.*, vol. 34, no. 3, pp. 31:1–14, 2015.

[17] S. Askew and G.V.G Baranoski, "On the dysfunctional hemoglobins and cyanosis connection: Practical implications for the clinical detection and differentiation of methemoglobinemia and sulfhemoglobinemia," *Biomed. Opt. Express*, vol. 9, no. 1, pp. 3284–3305, 2018.

[18] G.V.G. Baranoski, A. Dey, and T.F. Chen, "Assessing the sensitivity of human skin hyperspectral responses to increasing anemia severity levels," *J. Biomed. Opt.*, vol. 9, no. 20, pp. 095002:1–14, 2015.

[19] G.V.G Baranoski, S.R. Van Leeuwen, and T.F. Chen, "On the detection of peripheral cyanosis in individuals with distinct levels of cutaneous pigmentation," in *39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Jeju Island, South Korea, July 2017, pp. 4260–4264.

[20] T.F. Chen and G.V.G. Baranoski, "A physiologically-based framework for the simulation of skin tanning dynamics," in *Proc. of SPIE, Vol. 10877, Dynamics and Fluctuations in Biomedical Photonics XVI: Tissue and Cell Dynamics, SPIE Photonics West - BiOS*, M.J. Leahy V.V. Tuchin and R.W. Wang, Eds., San Francisco, CA, USA, March 2019, pp. 108770H–1–20.

[21] S.R. Van Leeuwen and G.V.G Baranoski, "Elucidating the contribution of Rayleigh scattering to the bluish appearance of veins," *J. Biomed. Opt.*, vol. 23, no. 2, pp. 025001–1–17, 2018.

[22] G.V.G. Baranoski, J.G. Rokne, and G. Xu, "Virtual spectrophotometric measurements for biologically and physically-based rendering," *The Visual Computer*, vol. 17, no. 8, pp. 506–518, 2001.

[23] Natural Phenomena Simulation Group (NPSG), *Run HyLIoS Online*, School of Computer Science, University of Waterloo, Ontario, Canada, 2017, http://www.npsg.uwaterloo.ca/models/hyliosEx.php.

[24] G.V.G. Baranoski, T. Dimson, T.F. Chen, B. Kimmel, D. Yim, and E. Miranda, "Rapid dissemination of light transport models on the web," *IEEE Comput. Graph.*, vol. 32, pp. 10–15, 2012.

[25] D.M. Hamby, "A review of techniques for parameter sensitivity analysis of environmental models," *Environ. Monit. Assess.*, vol. 32, pp. 135–154, 1994.

[26] D.M. Hamby, "A comparison of sensitivity analysis techniques," *Health Physics*, vol. 68, pp. 195–204, 1995.

[27] F.O. Hoffman and R.H. Gardner, "Evaluation of uncertainties in radiological assessment models," in *Radiological Assessment A Textbook on Environmental Dose Analysis*, J.E. Till and H.R. Meyer, Eds., Washington, DC, USA, 1983, pp. 1–55, U.S. Nuclear Regulatory Commission, NRC FIN B0766.

[28] E.A. Genina, A.N. Bashkatov, A.A. Korobko, E.A. Zubkova, and V.V. Tuchin, "Optical clearing of human skin: comparative study of permeability and dehydration of intact and photothermally perforated skin," *J. Biomed. Opt.*, vol. 13, no. 2, pp. 021102:1–8, 2008.

[29] R.M. Lavker, P. Zheng, and G. Dong, "Aged skin: A study by light, transmission electron, and scanning electron microscopy," *J.Invest. Dermatol.*, vol. 88, pp. 44–51, 1987.

[30] R. Wong, S. Geyer, W. Weninger, J. Guimberteau, and J.K. Wong, "The dynamic anatomy and patterning of skin," *Exp. Dermatol.*, vol. 25, pp. 62–98, 2015.