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Monte Carlo simulations to investigate light coupling with optical skin phantom

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Monte Carlo simulations to investigate light coupling with optical skin phantom

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"Life is not easy for any of us. But what of that? We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained." Marie Curie

ABSTRACT

FORTUNATO,T.C. Monte Carlo simulations to investigate light coupling with optical skin phantom. 2021. 119p. Thesis (Doctor in Science) - Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2021.

The effects observed during the light interaction with the most varied biological tissues make light an interesting tool for both diagnostic and therapeutic purposes. For a particular biomedical optical technique to be successful, it is essential to know and understand how the light interacts with the target tissue. Experimental measurements, theoretical modeling and computational simulations are widely used to improve the understanding of how light can interact with a tissue. The Monte Carlo simulations are considered important and reliable tools for detailed studies on the light propagation in tissue. It is known that to analyze the propagation of light in biological tissues we should take into account many factors, such as tissue optical properties, light source characteristics, interface roughness and illuminated tissue composition. In this context, in this thesis we used an optimized computational simulation method, Monte Carlo eXtreme (MCX), to predict the changes in the propagation of 630 nm light beam when a layer of a transparent material with different refraction indexes and thicknesses is added between the air and the surface of a homogeneous turbid medium (human dermis phantom) and a multi-layer (human skin phantom). We explored the effects caused by the transparent material when the light beam angle of incidence was varied and also when multiple sources are combined. Lastly, the material's refractive index was extrapolated in order to obtain a mirror-like object on the skin phantom surface. The simulations demonstrated that the phantom structures and optical properties, as well as the incident light beam geometry (angle of incidence) highly influence the light propagation, and that using a transparent material between the air and the phantom we can create a more uniform field of illumination, however, the observed effects are also dependent on the material thickness and refractive index. A mirror-like object also led to a significant change in the photon flux. The observed results are due, in large part, to the phenomena of refraction and total internal reflection of the light scattered by the phantom. The presented results showed that MCX is a useful tool for more fundamental studies towards a better understanding on the light propagation in biological tissues according to different irradiation strategies. It can also help to path the way to the personalization of light dosimetry dosimetry in clinics.

Keywords: Light distribution. Monte Carlo simulations. Monte Carlo eXtreme. Turbid media. Phototherapies. Photodiagnosis.

RESUMO

FORTUNATO,T.C. Simulações de Monte Carlo para investigação de acoplamento de luz a *phantom* óptico de pele. 2021. 119p. Thesis (Doctor in Science) - Instituto de Física de São Carlos, Universidade de São Paulo, São Carlos, 2021.

Os efeitos observados durante a interação da luz com os mais diversos tecidos biológicos tornam a luz uma ferramenta interessante tanto para fins diagnósticos quanto terapêuticos. Para que uma determinada técnica ótica biomédica tenha sucesso, é essencial conhecer e compreender como de com a luz interage com o tecido-alvo. Medidas experimentais, modelagem teórica e simulações computacionais são amplamente utilizadas para melhorar a compreensão de como a luz pode interagir com um tecido. As simulações de Monte Carlo são consideradas ferramentas importantes e confiáveis para estudos detalhados sobre a propagação da luz no tecido. Sabe-se que para analisar a propagação da luz em tecidos biológicos devemos levar em consideração diversos fatores, como propriedades ópticas do tecido, características da fonte de luz, rugosidade da interface e composição do tecido iluminado. Neste contexto, nesta tese foi utilizado um método de simulação computacional otimizado, Monte Carlo eXtreme (MCX), para prever as mudanças na propagação do feixe de luz com o comprimento de onda de 630 nm quando uma camada de um material transparente com diferentes índices de refração e espessuras é adicionada entre o ar e a superfície de um meio túrbido homogêneo (phantom da derme humana) e de um multicamadas (phantom da pele humana). Exploramos os efeitos causados pelo material transparente quando o ângulo de incidência do feixe de luz era variado e quando fontes múltiplas são combinadas. Por último, o índice de refração do material foi extrapolado a fim de obter um objeto semelhante a um espelho na superfície do phantom de pele. As simulações demonstraram que as estruturas e propriedades ópticas do phantom, bem como a geometria do feixe de luz incidente (ângulo de incidência) influenciam fortemente a propagação da luz e que usando um material transparente entre o ar e o phantom podemos criar um campo de iluminação mais uniforme, no entanto, os efeitos observados também dependem da espessura desse material e do índice de refração. O objeto semelhante a espelho também levou a uma mudança significativa no fluxo de fótons. Os resultados observados são devidos, em grande parte, aos fenômenos de refração e reflexão interna total da luz espalhada no phantom. Os resultados apresentados mostraram que o MCX é uma ferramenta útil em estudos mais fundamentais para um melhor entendimento da propagação da luz em tecidos biológicos de acordo com diferentes estratégias de irradiação. Também pode ajudar a traçar o caminho para a personalização da dosimetria da luz na clínica.

Palavras-chave: Distribuição de luz. Simulações de Monte Carlo. Monte Carlo eXtreme. Meios túrbidos. Fototerapias. Fotodiagnóstico..

LIST OF FIGURES

Figure 1 –	Snell law's diagram.	26
Figure 2 –	Schematic representation of light-tissue interaction phenomena	27
Figure 3 –	Flowchart of the Monte Carlo simulations to calculate photon trajectories.	29
Figure 4 –	Block diagram of the parallel Monte Carlo simulation for photon propagation.	31
Figure 5 –	An example of equipment for light therapy with different light source ge-	
	ometries	33
Figure 6 –	Example of various types of skin	33
Figure 7 –	Simulation setup with homogeneous phantom	35
Figure 8 –	MC simulation of photon flux in homogeneous phantom along plane $y =$	
	0 mm, when $h_{ca} = 1$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7,$	
	1.8 and 1.9. The dashed line represents the phantom top surface. For better	
	visualization, logarithmic scale is used	38
Figure 9 –	MC simulation of photon flux in homogeneous phantom along plane $y =$	
	0 mm, when $h_{ca} = 3$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7,$	
	1.8 and 1.9. The dashed line represents the phantom top surface. For better	
	visualization, logarithmic scale is used	39
Figure 10 –	MC simulation of photon flux in homogeneous phantom along plane $y = 0$	
	mm, when $h_{ca} = 3 \text{ mm}$ and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$	
	and 1.9. The dashed line represents the phantom top surface. Contour curves	
	(black lines) are used for better follow the shape of a photon flux value	40
Figure 11 –	Comparison of $\log_{10} (flux) = -3$ curves in homogeneous phantom for the	
	different thicknesses and refractive indices of the simulated CA along plane	
	y = 0 mm	41
Figure 12 –	Scheme of the area (green region) under the $\log_{10} (flux)$ curves	41
Figure 13 –	Comparison between different h_{ca} of calculated areas of $\log_{10} (flux)$ curves	
	normalized by the are when $n_{ca} = 1$. Each line in the graphs corresponds to	
	a different value of n_{ca} . Values above the dashed line indicates an increase	
	in the area when the CA was added	42
Figure 14 –	Comparison of the area as a function of n_{ca} for $\log_{10} (flux) = -3$ curve for	
	$h_{ca} = 1, 2, 3$ and 4 in homogeneous phantom. The dashed line corresponds	
	to the value of area when $n_{ca} = 1$.	43
Figure 15 –	Photon flux as a function of depth (z) when $h_{ca} = 3$ mm, for all simulated	
	n_{ca} in a homogeneous phantom	43
Figure 16 –	MC simulation of photon flux in homogeneous phantom along plane $z = 5.5$	
	mm, when $h_{ca} = 1 \text{ mm}$ and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and	
	1.9	44

Figure 17 –	MC simulation of photon flux in homogeneous phantom along plane $z = 5.5$ mm, when $h_{ca} = 4$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and	
Figure 18 –	1.9	44
C	tance between the blue and black dot	45
Figure 19 –	Log ₁₀ (<i>flux</i>) as function of x position at $y = 0$ mm and $z = 5.5$ mm, for all h_{ca} simulated: (a) 1 mm, (b) 2 mm, (c) 3 mm and (d) 4 mm	46
Figure 20 –	Rings width according to the CA thickness.	47
Figure 21 –	Snell's law schematics showing: (a) light beam refraction when $n_2 > n_1$; (b) when $n_2 < n_1$, refraction occurs, but for angles of incidence larger that the aritical angle (θ_1) total internal reflaction occurs	17
Figure 22 –	Correlation between critical angle and n_{ca} at the interfaces present in the simulations. Red squares correspond to the interface between the CA and the air, blue circles correspond to the interface between the phantom and the CA, and the yellow triangles correspond to the interface between the CA and the phantom. The green line corresponds to the phantom refractive index	48
Figure 23 –	Skin tissue layers model.	51
Figure 24 –	Schematics of the multi-layered skin phantom structure used in this chapter.	52
Figure 25 –	Random matrix generated to simulate irregularities map of epidermis, the black color represent the air and white a epidermis.	53
Figure 26 –	Schematics used to calculate the displacement of the light source required to position the beam in the center of the phantom surface.	55
Figure 27 –	Schematics of the four sources (red dots) location in the xy plane	56
Figure 28 –	MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane y=0 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$, 1.3, 1.4, 1.5 and 1.6. Contour curves (black lines) are used for better follow the shape of a photon flux value	57
Figure 29 –	MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane y=0 mm, when $h_{ca} = 3.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6. Contour curves (black lines) are used for better follow the shape of a photon flux value	58
Figure 30 –	Comparison of $\log_{10} (flux) = -3$ curves in a multi-layered skin phantom with smooth epidermis for the different thicknesses and refractive indices of	50
	the simulated CA along plane $y = 0$ mm	59
Figure 31 –	Comparison of the area as a function of n_{ca} when $\log_{10} (flux) = -3$ for $h_{ca} = 1.04, 2.00, 3.04$ and 4.00 mm in multi-layered phantom with smooth	
	epidermis. The dashed line corresponds to the value of area when $n_{ca} = 1$.	59

Figure 32 –	MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane z=5.2 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3$,	(0)
Figure 33 –	1.4, 1.5 and 1.6	60
Figure 34 –	and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6	60
	epidermis filled with CA along plane $z = 5.2$ mm (epidermis layer), when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6.	61
Figure 35 –	MC simulation of photon flux in multi-layered skin phantom with irregular epidermis filled with air and CA above along plane z=5.2 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6.	61
Figure 36 –	MC simulation of photon flux in multi-layered skin phantom with irregular epidermis filled with water and CA above along plane $z = 5.2$ mm, when $h_{-} = 1.04$ mm and $n_{-} = 1.0, 1.3, 1.4, 1.5$ and 1.6	61
Figure 37 –	$n_{ca} = 1.04$ min and $n_{ca} = 1.0, 1.5, 1.4, 1.5$ and 1.0	63
Figure 38 –	Comparison of the local entropy integration as function of n_{ca} for first layer of papillary dermis ($z = 5.28$ mm) for the different interface features evalu- ated.	63
Figure 39 –	Comparison of the local entropy integration as function of n_{ca} for second layer of papillary dermis ($z = 5.36$ mm) for the different interface features evaluated	64
Figure 40 –	Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis $(z = 5.2 \text{ mm})$ when $h_{ca} = 1.04 \text{ mm}$ for $n_{ca} = 1.3, 1.4, 1.5$ and 1.6.	65
Figure 41 –	Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis $(z = 5.2 \text{ mm})$ when $h_{ca} = 2.00 \text{ mm}$ for $n_{ca} = 1.3, 1.4, 1.5$ and $1.6, \ldots, \ldots$	65
Figure 42 –	Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis $(z = 5.2 \text{ mm})$ when $h_{ca} = 3.04 \text{ mm}$ for $n_{ca} = 1.3, 1.4, 1.5$ and $1.6, \ldots, \ldots, \ldots$	65
Figure 43 –	Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis $(z = 5.2 \text{ mm})$ when $h_{ca} = 4.00 \text{ mm}$ for $n_{ca} = 1.3, 1.4, 1.5$ and $1.6, \ldots \ldots \ldots \ldots$	65
Figure 44 –	Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer ($z = 7.12$ mm) when $h_{ca} = 1.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis	
Figure 45 –	is a smooth	66
	is a smooth. $\dots \dots \dots$	66

Figure 46 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer ($z = 7.12$ mm) when $h_{ca} = 3.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis	
is a smooth.	66
Figure 47 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer ($z = 7.12$ mm) when $h_{ca} = 4.00$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis	
is a smooth.	67
Figure 48 – Flux decay as function of z for $x = 0, 4, 8$ and 12 mm and $y = 0$ mm with	
$h_{ca} = 1.04$ mm and smooth epidermis condition.	67
Figure 49 – Reflection coefficient as a function of the incidence angle for the multi-	
layered skin phantom, (a) in the light incidence direction and (b) in the	
oposite direction, at each interface of the skin phantom	68
Figure 50 – Reflection coefficient with incidence angle for the n_{ca} simulated, in (a) CA-	
epidermis direction, in (b) epidermis-CA and (c) CA-air	69
Figure 51 – MC simulation of photon flux in multi-layered skin phantom along plane	
$y = 0$ mm for different incidence angle, when $h_{ca} = 1$ mm for n_{ca} = 1.0	70
Figure 52 - MC simulation of photon flux in multi-layered skin phantom along plane	
$y = 0$ mm for different incidence angle, when $h_{ca} = 1$ mm for $n_{ca} = 1.3.$.	71
Figure 53 – Comparison of $Flux = 0.3$ curve inside the multi-layered skin phantom	
along $y = 0$ mm plane for different indices angles. The top graph is the air	
condition and bellow is $n_{ca} = 1.3.$	71
Figure 54 – Schematics of the procedure used to calculate Δz and Δx	72
Figure 55 – Δz (left axis) and Δx in the epidermis (right axis) as function of incidence	
angle for flux=0.3 when $h_{ca} = 1.04$ mm	72
Figure 56 – MC simulations of photon flux in multi-layered skin phantom along plane	
$z=0~\mathrm{mm}$ for each source used to compose the array when $d=0.48~\mathrm{mm}.$ $~$.	73
Figure 57 – MC simulations of photon flux in multi-layered skin phantom along plane	
z = 0 mm for light sources sum when $d = 0.48$ mm	73
Figure 58 – MC simulations of photon flux in multi-layered skin phantom along $z = 5.2$	
mm (epidermis layer) when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and	
1.6	74
Figure 59 – MC simulations of photon flux in multi-layered skin phantom along each	
skin layer simulate when $h_{ca} = 1.04 \text{ mm}$ and $n_{ca} = 1.0. \dots \dots \dots$	75
Figure 60 – MC simulations of photon flux in multi-layered skin phantom along each	
skin layer simulate when $h_{ca} = 1.04 \text{ mm}$ and $n_{ca} = 1.0. \dots \dots \dots$	76
Figure 61 – Photon flux as function of z at $x = 0$ mm and $y = 0$ mm when $h_{ca} = 1.04$	
mm in (a) $d = 0.48$ mm, (b) $d = 1.52$ mm, (c) $d = 2.48$ mm, (d) $d = 3.52$ mm	77
Figure 62 – Surface plot of $\log_{10} (flux) = -3$ for the different distances d, comparing	
all n_{ca} simulated.	78

Figure 63 –	Schematics of the simulation setup used for reflective material optical prop-	
	erties validation.	81
Figure 64 –	Schematics of the simulation setup for the reflective material simulations.	82
Figure 65 –	Monte Carlo simulation for validation of total reflective material. The white	
	lines correspond to reflective material interfaces	83
Figure 66 –	MC simulations of photon flux in multi-layered skin phantom for the condi-	
	tions: without reflective material, $r_m = 0.48 \text{ mm}$ and $r_m = 3.12 \text{ mm}$	83
Figure 67 –	Comparison of the logarithm scale photons flux curves for the values -3 to 1	
	with 0.5 variation for all reflective radius analyzed.	84
Figure 68 –	Comparison of number of photons detected by detectors 1 and 2 as function	
	of the reflective radius.	84
Figure 69 –	Rate of increase in the number of photons detected with respect to control	
	versus the reflective radius.	85
Figure 70 –	MC simulation of photon flux along plane y=0 mm without CA. In (a) is the	
	homogeneous phantom and in (b) a multi-layered skin phantom.	88

LIST OF TABLES

Table 1 –	Simulation parameters for the homogeneous medium	36
Table 2 –	Summary of the parameters used in the simulations	37
Table 3 –	Skin optical proprieties used in the simulations	52
Table 4 –	General parameters used for simulations of multi-layered tissue phantom	54
Table 5 –	Coordinates of the different simulated sources.	56
Table 6 –	Optical properties used in the simulations	81

LIST OF ABBREVIATIONS AND ACRONYMS

RTE Radiative transport equation Transmission phenomenon Т Scattering phenomenon S Absorption phenomenon А MC Monte Carlo MCX Monte Carlo eXtreme Graphics processing unit GPU Compute unified device architecture CUDA Monte Carlo eXtreme for MATLAB® MCXLAB CA Coupling agent Optical phantom PH Total internal reflection TIR

LIST OF SYMBOLS

R_s	Specular reflection
$ heta_1$	Incidence angle
R_d	Diffuse reflaction
С	Light speed in vacuum
v_1	Light speed in incident medium
v_2	Light speed in refracted medium
θ_1'	Reflection angle
n	Refractive index
n_1	Refractive index in the incident medium
n_2	Refractive index in the refracted medium
I_0	Incident light beam intensity
L	Radiance
\vec{r}	Position
Ω	Direction
t	Time
L_0	Initial radiance
μ_a	Absorption coefficient
μ_s	Scattering coefficient
g	Anisotropy factor
μ_t	Transport coefficient
p	Scattering phase
Q	Volumetric light source
Р	Raw probability
E_a	Absorbed energy

E_t	Total energy
ΔV	Voxel volume
Δt	Time step
h_{ca}	Coupling agent thickness
n_{ph}	Refractive index of phantom
n_{ca}	Refractive index of coupling agent
d	Source distance from the medium center
М	Resulting matrix
m_i	Value of interest
fesc	Voxel resolution
w_{ring}	Ring width

CONTENTS

1		25
1.1	Fundamentals of the light interaction with biological tissues	25
1.1.1	Radiative transport equation	28
1.1.2	Monte Carlo	28
2	MOTIVATION AND GOALS	33
2.1	Motivation	33
2.2	Goals	34
3	TRANSPARENT LAYER OVER HOMOGENEOUS DERMIS PHAN-	
	ТОМ	35
3.1	Simulated conditions	35
3.2	Hardware	37
3.3	Results	37
3.4	Conclusion	49
4	TRANSPARENT LAYER OVER MULTI-LAYERED SKIN PHANTOM	51
4.1	Simulated condition	51
4.1.1	Turbid medium	51
4.1.2	Light source with normal incidence	53
4.1.3	Light source with oblique incidence	55
4.1.4	Multiple light sources	55
4.2	Results and discussion	57
4.2.1	Light source with normal incidence	57
4.2.2	Light source with oblique incidence	70
4.2.3	Multiple light sources	73
4.3	Conclusions	78
5	A MIRROR-LIKE OBJECT OVER MULTI-LAYERED SKIN PHANTOM	81
5.1	Simulated conditions	81
5.2	Results and discussion	82
5.3	Conclusions	85
6	FINAL CONSIDERATIONS AND CONCLUSIONS	87
6.1	Final considerations	87
6.2	Conclusions	90

	REFERENCES	91
	APPENDIX	95
	APPENDIX A – CHAPTER 3 SCRIPTS	97
A.1	Main code	97
A.2	Simulation execution	99
	APPENDIX B – CHAPTER 4 SCRIPTS	101
B.1	Creating the simulated volume	101
B.2	Simulation script for a normal incidence	102
B.3	Simulation script for oblique incidence	105
B.4	Simulation script for multiple sources	108
	APPENDIX C – CHAPTER 5 SCRIPTS	113
C.1	Script for reflective material optical properties validation	113
C.2	Volume inicialization	114
C.3	Simulation script	115

1 INTRODUCTION

The use of light in healthcare has become increasingly widespread. The effects observed during the interaction of light with the most varied biological tissues make it an interesting tool for both diagnostic and therapeutic purposes.^{1,2} These effects will depend on the characteristics of the light source (wavelength, intensity, interaction time, etc.) and the optical properties of the target tissue (absorption, scattering, and anisotropy coefficients, among others).

For a successful application of a biomedical optics technique, it is essential to know and understand how the light interacts with the target tissue, as well as to know all the variables that may influence the application.

Experimental measurements, theoretical modeling, and computational simulations are widely used to improve the understanding of how light can interact with a tissue. Monte Carlo simulation have been considered an important and reliable tool for detailed studies on the light propagation in biological tissues.

1.1 Fundamentals of the light interaction with biological tissues

Light can be described as an electromagnetic wave or as a particle (photon). When we interpret light as a wave, the wavelength range in which we consider the light as visible is between 400 nm to 700 nm.³

Biological tissues are turbid media (characterized by scattering and absorption) and the light propagation within these media can be described using Maxwell's equations. This description is a rigorous model for the propagation of electromagnetic waves and takes all phenomena into account such as interference, diffraction, and polarization, and has high reliability at all spatial scales, however, its solution requires a high computational cost.⁴

Another way to describe this propagation is using the corpuscular nature of light, considering it as a set of photons and using the radiative transport equation (RTE).⁵

When a light beam hits the surface of biological tissue, several phenomena can be observed. If the tissue surface is smooth enough, such that the irregularities are small when compared to the wavelength of the incident light, the phenomenon of specular reflection (Rs) will occur, in which the angle of incidence (θ_1) is equal to the angle of reflection. When the surface has irregularities of the same order of magnitude or greater than the wavelength of the incident light, like most biological tissues, diffuse reflection (Rd) occurs.

Thinking about the case in which incident light passes through the surface that separates two media of different refractive indexes (figure 1), such as air-tissue, refraction is observed, a phenomenon originated from the change in the speed of light propagation in the medium. Refraction is described by Snell's law (equation (1.1)) where θ_1 is the incident angle, θ_2 the refraction angle, v_1 and v_2 the speed of light in the medium 1 (incidence medium) and 2 (refraction medium) respectively.



Figure 1 – Snell law's diagram. Source – By the author.

$$\frac{\sin \theta_1}{\sin \theta_2} = \frac{v_1}{v_2} \tag{1.1}$$

A usual way of determining refringence is the magnitude called refractive index, a quantity that describes how fast light travels through a material, it is represented by n defined by the ratio of the speed of light in vacuum c and the speed of light in the material v.

$$n = \frac{c}{v} \tag{1.2}$$

Thus, using this quantity, n_1 for the incident medium and n_2 for the refractive medium, we can determine how much light deviates when entering a certain material, which brings us to the equation (1.3) this other way of Snell's law.

$$n_1 \sin \theta_1 = n_2 \sin \theta_2 \tag{1.3}$$

It is worth noting that for $\sin \theta_1 > \frac{n_2}{n_1}$, the equation (1.3) is not satisfied for real values of θ_1 if $n_1 > n_2$ and total reflection occurs.

Part of the light can also pass through all the tissue emerging from the opposite interface, defining the phenomenon of transmission (T).

Photons traveling within a biological tissue can interact with scatterers (e.g., membranes, intracellular organelles, collagen fibers) which will change the direction of light propagation which is called the scattering phenomenon (S). They can also interact with absorbing agents (e.g., hemoglobin, melanin), which will cause the absorption phenomenon (A), in which light is converted into heat, fluorescence, phosphorescence, chemical reactions, etc. As a biological tissue has both scattering and absorption, it is called these turbid media. Figure 2 illustrates the main light interactions with a homogeneous biological medium.⁶



Figure 2 – Schematic representation of light-tissue interaction phenomena. Source – By the author.

Thus, considering the conservation of the number of photons affecting a tissue (I_0) , we can write equation (1.4), where I_0 is the incident light beam intensity, R_s is the specular reflection, and R_d diffuse reflection.

$$I_0 = R_s + R_d + A + T. (1.4)$$

In the RTE, the assessed quantity will be the radiance, $L(\vec{r}, \hat{\Omega}, t)$ [W/mm²sr] which is the radiant flux per unit of projected area per solid angle. Next, we will discuss the effects of absorption and scattering on this quantity.

When light enters into an absorbing medium, as it propagates through the tissue thickness, the radiance will decay exponentially with the distance of propagation according to Beer's law, given by equation (1.5), where L_0 is the initial radiance and μ_a is the absorption coefficient in mm⁻¹ and z is the distance. Thus, after the absorption, the photon will stop its propagation.⁶

$$L\left(z\right) = L_0 \mathrm{e}^{-\mu_a z} \tag{1.5}$$

In the case of a scattering medium, the radiance also decays exponentially, given by equation (1.6), where μ_s is the scattering coefficient in mm⁻¹, after being scattered a photon will continue to propagate in a new direction.⁶

$$L(z) = L_0 \mathrm{e}^{-\mu_s z} \tag{1.6}$$

To describe the whole scattering phenomenon, we need to define another property, the anisotropy coefficient (g). It represents the average direction in which the photon is scattered. When g = 1, it means that the scattering is purely forward, when g = -1 the scattering is purely backward, and g = 0 the scattering is isotropic. In equation (1.7) there is its definition, that is

given by the average of the $\cos \theta$ being θ the direction of scattering, $d\Omega$ solid angle element and $p(\theta)$ probability function.

$$g = \frac{\int_{4\pi} p(\theta) \cos \theta d\Omega}{\int_{4\pi} p(\theta) d\Omega}$$
(1.7)

As already mentioned, part of the light can be redirected and continue propagating. To describe all the effects and to calculate the light distribution in the medium, it is necessary to use the radiative transport equation $(RTE)^5$ that will be better addressed in the following section.

1.1.1 Radiative transport equation

Considering the corpuscular nature of light, we can describe its spatial and temporal propagation using equation (1.8),⁵ known as radiative transport equation. Where μ_t is the transport coefficient that comprises the sum of the scattering and absorption coefficients: $\mu_t = \mu_s + \mu_a$. The variable $p\left(\hat{\Omega}^{\epsilon} \to \hat{\Omega}\right)$ is the scattering phase function and $Q\left(\vec{r}, \hat{\Omega}, t\right)$ is the volumetric light source in units of [W/mm³ sr].

$$\underbrace{\frac{1}{v}\frac{\partial}{\partial t}L\left(\vec{r},\hat{\Omega},t\right)}_{1} = \underbrace{-\hat{\Omega}\cdot\nabla L\left(\vec{r},\hat{\Omega},t\right)}_{2} - \underbrace{\mu_{t}L\left(\vec{r},\hat{\Omega},t\right)}_{3} + \underbrace{\mu_{s}\int_{4\pi}L\left(\vec{r},\hat{\Omega}',t\right)p\left(\vec{r},\hat{\Omega}'\rightarrow\hat{\Omega}\right)d\hat{\Omega}'}_{4} + \underbrace{Q\left(\vec{r},\hat{\Omega},t\right)}_{5} +$$

Analyzing the terms separately, we have on the left side the rate of change of radiance over time (term 1). Term 2 is highlighted by the loss of radiance due to transmission, and term 3 is the loss due to scattering and absorption in a certain direction. Term 4 represents a gain due to scattering from all other directions, and term 5 is related to the light source used.

There are some types of approximations to solve the RTE, one of them is the diffusion approximation, in which the absorption coefficient μ_a is considered much lower than scattering μ_s , this regime being valid only in regions far from the light source. For studies of light propagation close to the source, it is necessary to use a more effective method, known as Monte Carlo simulations.⁷

1.1.2 Monte Carlo

The current gold standard method for solving RTE is the Monte Carlo numerical integration method (MC).^{7–9} This is a statistical method that computationally simulates the random trajectory of individual photons. Being N the number of simulated photons, the precision is proportional to \sqrt{N} , the result will be valid since it considers a large N.⁶

The key idea of the MC simulations applied to the absorption and scattering phenomena is to follow the optical path of a photon through the turbid medium. For this, it is taken into consideration 5 basic steps: generation of photons from a source, generation of paths, absorption, elimination, and detection.^{6, 10} The flowchart in figure 3 illustrates the basic steps of MC simulations.



Figure 3 – Flowchart of the Monte Carlo simulations to calculate photon trajectories. Source – Adapted from FORTUNATO.¹¹

The distance between the distance between two scattering or absorption events is selected from a logarithmic distribution, using a computer-generated pseudo-random number. Absorption is counted by assigning a weight to each photon and that weight is reduced during propagation. With scattering, a new direction of propagation is chosen according to the phase function and another pseudo-random number generated by the computer. The entire process continues until the photon escapes the volume considered, until it is absorbed or until its weight reaches a certain cut-off value.⁷ After repeating the steps until it simulates all N photons, the path map is stored in the computer. Thus, it is possible to infer what happened to the light that propagated in that environment.

As the accuracy of the method is greater as higher the number of simulated photons, the MC methods are often considered very time-consuming, however, in recent years a series of optimized implementations combined with more powerful hardware have emerged and reduced the processing time from several hours to a couple of minutes.

There are some optimized Monte Carlo implementations already available in literature, such as MCML,^{12,13} MCCL,¹⁴ ValoMC¹⁵ among others. One implementation that has been gaining ground in recent years is the MCX - Monte Carlo eXtreme presented for the first time in 2009 by Fang and Boas.¹⁶ MCX is being developed to be simple to use and to be optimized due to the use of a graphic processing unit (GPU). In Yu *et al.*¹⁷ a speedup analysis of the MCX simulations was made comparing different computational devices and showed the advantage of using graphics processors for the simulations.

A GPU is a specialized microprocessor for graphics processing because it is made to process large blocks of information in parallel. GPU was introduced in the personal computer market in 1999 by the company Nvidia (California, USA).¹⁸ Over the years and parallel computing, GPUs came to be used for scientific calculus. Nvidia[®] has realized this interest among the academic community and in 2007 released a parallel computing platform called CUDA, from which the MCX implementation was built.^{19,20}

Currently, with the popularization of graphics cards for scientific propose, GPUs have emerged from other companies, such as AMD (California, USA). In this case, the program must be implemented using OpenCL instead of CUDA. However, in some applications, the use of CUDA and GPU Nvidia has better performance.

In figure 4, we have the block diagram shown by Fang¹⁶ on the MCX implementation. For each subprocess, a photon is initialized and its trajectory is calculated. A very important part of this implementation is the use of global memory for all threads, in that memory the process stores the accumulation of probability in each position and reads the properties (μ_s , μ_a , g and n) of the position being analyzed.



Figure 4 – Block diagram of the parallel Monte Carlo simulation for photon propagation. Source – FANG; BOAS.¹⁶

After the initialization of a photon, the scattering length is calculated, then it is moved to the next voxel (spatial volume element). At this point the attenuation is calculated from the absorption, getting the raw probability at that given volume, this step is repeated until the photon reaches the distance of scattering. Then, the new direction of scattering is obtained by calculating the azimuth angle and zenith through generation of a pseudo-random number uniformly using the Henyey-Greenstein phase function (equation (1.9)).⁶ The previous step is repeated while the photon exists or until he leaves the medium.¹⁶

$$p(\theta) = \frac{1 - g^2}{\left(1 + g^2 - 2g\cos\theta\right)^{3/2}}$$
(1.9)

The implementation is based on the energy conservation to normalize the accumulated raw probability in the volume, as shown in equation (1.10)

$$F(\vec{r},t) = P(\vec{r},t) \frac{\frac{E_a}{E_t}}{\sum_i \sum_j P(\vec{r}_i,t_j) \mu_a(\vec{r}_i) \Delta V \Delta t}$$
(1.10)

where $P(\vec{r}, t)$ is the raw probability (unitless) in a given spatial position (\vec{r}) and time (t), $\frac{E_a}{E_t}$ is the percentage of the total energy absorbed by the medium, ΔV is the volume of the voxel and Δt is the time step. The output is the fluence distribution for a time step in $(mm^{-2}s^{-1})$. This implementation also considers the interface effects due to the change in the refractive index using Fresnel relations.¹⁶ MCX has the advantage of easily implement objects of different geometries through a cubic matrix with different indexes and optical coefficients. The light source can also be easily changed according to its shape, position, incident angle. These features of MCX make it possible to study light propagation in biological tissues in a large variety of conditions that have not been explored yet.²¹

2 MOTIVATION AND GOALS

2.1 Motivation

In Biomedical Optics applications, either for therapy or for diagnostics, it is important to establish the best strategy for tissue irradiation. The main difficulties rely on the fact that there are several types of equipment and several types of target tissues.

Regarding equipment, even when they have similar purposes, they are built with different specifications, such as light beam profile, spot size, delivery mode (at a distance or in contact, continuous or pulsed), single-source, or array of sources. Figure 5 shows an example of a commercial equipment for phototherapies that has different probes with different geometries.



Figure 5 – An example of equipment for light therapy with different light source geometries. Source – THOR.²²

Regarding the target tissue, this may vary from site to site and from patient to patient: the skin color, the thickness of the layers, the roughness of the surface, the hydration, etc. We can see an example of this diversity in figure 6. The importance of studying light propagation in the skin is because it is the most exposed part of the body, and is the first barrier of the body for most of the photodiagnosis techniques, phototherapies, and photodynamic therapy applications.



Figure 6 – Example of various types of skin. Source – NEEDPIX.²³

It is noticeable that the best strategy of irradiation is not very simple to determine, and up to our knowledge, the influence of all these different parameters (technological or biological) has not been deeply explored yet. It is not clear how light dosimetry for a certain phototherapy, for instance, can be affected by the tissue surface roughness, or by the application of a cream or oil during the irradiation. Previous works from our research group, the use of coupling materials to change the light distribution was analyzed in *in-vitro* experiments, that analyzed the use of a carbopol gel on the rough surface of a solid turbid phantom with the light source inside the gel and measured the distribution inside the medium. The authors showed that the gel was able to attenuate the effects caused by the roughness surface on the light distribution within the phantom.²⁴

Since 1989 with Flock *et al.*⁷ Monte Carlo simulations have been used to predict light propagation through biological tissue. Excellent results have been obtained, and this motivated us to think about MC as the best option to better understand light propagation and to use it for dosimetric purposes.

The biggest obstacle to the establishment of individualized light dosimetry is that experimental measurements of all the features of a target tissue would require an invasive procedure, like the insertion of an optical fiber, and it is infeasible and impractical.

2.2 Goals

In this context, this thesis aims to use Monte Carlo simulations to analyze changes in the propagation of 630 nm light when a material is added on the surface of an optical phantom.

For this purpose, we divided the studies into three chapters: Transparent layer over homogeneous turbid medium (chapter 3); Transparent layer over multi-layered skin phantom (chapter 4) and A mirror-like object over multi-layered skin phantom (chapter 5).

In chapter 3, we performed simulations adding the transparent medium on the surface of a homogeneous phantom with human dermis optical properties, and the effects of thickness and refractive index variation were studied.

In chapter 4 instead of a homogeneous phantom, we used a multi-layered phantom with human skin optical properties. The effects promoted by a smooth or irregular epidermis were also evaluated, as well as different light source setups: light beam with normal incidence, light beam with oblique incidence, and a set of four light sources in different positions.

Finally, in chapter 5, a highly reflective material was added on the surface of the skin phantom, and simulations were performed to investigate the effects caused by different sizes of the reflective material in the light propagation within the phantom.
3 TRANSPARENT LAYER OVER HOMOGENEOUS DERMIS PHANTOM

This part of the study aims to investigate the light distribution by Monte Carlo simulations in a homogeneous optical phantom when a transparent material is placed on its incidence surface. In this configuration, the incident light travels through the air and the transparent material before reaching the phantom surface and continues to propagate.

3.1 Simulated conditions

For this study, we used the compiled version of MCX for MATLAB[®] in a "mex" extension, MCXLAB, which according to the developers has similar performances to the commandline version of MCX. The advantage of this version is that the role of the simulation's input configuration can be sent through a MATLAB routine. All description of this function is in MCXLAB github directory.²¹ The MCX version used was v2017.7. It is important to note that during the development of this work; the MCX received several updated versions, and with this, it is more and more complete with more options of definitions for the elaboration of simulations.

MATLAB[®] routines (appendices A.1 and A.2) were developed in which a loop was made to create each configuration and the respective execution. The routines were also responsible for storing the results in a file of extension "mat" and write a log file with the simulations parameters and their execution times. The simulation volume was (32,32,15.5) mm³, where a homogeneous tissue optical phantom was placed at z = 5.5 mm with (32, 32, 10) mm³ volume and the voxel resolution used was 0.25 mm³. The optical properties of the phantom were set as the same of the human dermis for a Caucasian person, for a 633 nm light source: $\mu_a = 0.27 \text{ mm}^{-1}$, $\mu_s = 18.7 \text{ mm}^{-1}$, g = 0.81 and n = 1.41.^{25,26}

On the top of the tissue phantom, a layer of a transparent material was added and its thickness and refractive index were varied. Since this layer was added to evaluate the effect of light coupling to the phantom, we refer to it as "coupling agent" (CA). The rest of simulation volume above the CA was filled with air, as seen in figure 7.



Figure 7 – Simulation setup with homogeneous phantom. Source – By the author.

The optical properties of the transparent media was set with $\mu_a = 10^{-5} \text{ mm}^{-1}$, $\mu_s = 0 \text{ mm}^{-1}$, g = 1 with the index of refraction (n_{ca}) ranging from 1.0 to 1.9, varying by 0.1. This very low absorption coefficient was used to allow the visualization of the photon flux within the phantom, since the calculation of photon flux is based on the absorbed energy, which means that if the absorption is zero, the simulation does not return any flux. Considering very low μ_a does not compromise the results of the simulations; this even approaches to a more realistic situation, since most of the transparent materials present a negligible but non-null μ_a value. The optical properties of the phantom and the coupling agent are summarized in table 1.

Medium	$\mu_a (\mathrm{mm}^{-1})$	$\mu_s (\mathrm{mm}^{-1})$	g	n	Thickness (mm)		
Phantom (PH)	0.27	18.7	0.81	1.41	10		
Coupling agent (CA)	10^{-5}	0	1	1.0-1.9	1 - 4		
Source – By the author.							

Table 1 – Simulation parameters for the homogeneous medium.

The light source was defined as "*disk*" (a pre-defined light source in the MCX data base for light source geometries) which is described as a uniform disk pointing to a certain direction and radius defined by the user. It was implemented with normal incidence at the position (0,0,0) mm and with a radius of 0.5 mm. The number of simulated photons was 10^8 that according to Cai and Lu,²⁷ the statistical error for this number of photons is 0.3%. As this study is analyzing continuous light sources, the parameters *tstep* and *tend* were equal to 5×10^{-9} , from examples provided by the developers.²⁸

A summary of the computational parameters and the description used for the simulations are in table 2.

Parameter	Value	Description		
cfg.seed	1.6483e+09	Seed for the random number generator.		
cfg.nphoton	10^{8}	The total number of photons to be simulated.		
cfg.unitinmm	0.25	Defines the length unit for a grid edge length.		
cfg.srcpos	[64, 64, 0]	The position of the source in grid unit.		
cfg.srcdir	[0,0,1]	Specifying the incident vector.		
cfg.srctype	'disk'	Type of source.		
cfg.srcparam1	[2, 0, 0, 0]	Source radius.		
cfg.issrcfrom0	0	First voxel is [1,1,1]		
cfg.tstart	0	Starting time of the simulation.		
cfg.tend	5e-9	Ending time of the simulation.		
cfg.tstep	5e-9	Time-gate width of the simulation.		
cfg.autopilot	1	Set automatically set threads and blocks in GPU.		
cfg.isreflect	1	Consider refractive index mismatch.		
cfg.isrefint	1	Enable reflection at interior boundary too.		
cfg.isspecular	1	Calculate specular reflection if source is outside.		
cfg.outputtype	ʻflux'	Output is the fluence rate.		
cfg.isnormalized	1	Normalize the output fluence to unitary source.		
Source – By the author				

Table 2 – Summary of the parameters used in the simulations.

Source – By the author.

For processing the simulations output data was used a MATLAB® version 2015a, because it is optimized for matrices manipulation.

3.2 Hardware

To perform all the simulations and data processing present in this thesis, it was used a personal computer from the following description: Intel[®] Core[™] i5-4460 processor, 16 GB RAM memory and an NVIDIA® Geforce® GTX 1070 GPU with 8 GB RAM memory.

3.3 Results

The simulation results were 3 dimensional matrices, wherein each element is the particle flux passing through the position $(1/mm^2)$. Some results are presented in logarithmic scale and it is necessary due to the difficulty of analyzing the flux in whole volume, since in distances close to the source it has a value of an order of magnitude higher than in distant regions, thus, using the logarithmic scale, we decreased this difference and improving the graphs contrast. In figures 8 and 9 we present the logarithm particles flux maps along plane y = 0 mm for the cases in which the CA thickness (h_{ca}) were 1 and 3 mm, respectively.



Figure 8 – MC simulation of photon flux in homogeneous phantom along plane y = 0 mm, when $h_{ca} = 1$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and 1.9. The dashed line represents the phantom top surface. For better visualization, logarithmic scale is used.

Source – By the author.

When $n_{ca} = 1$, we were assuming that only air is on the top of the tissue phantom, in this way, in figure 8, the result for $n_{ca} = 1$ can be considered as a control result. It is observed that when the n_{ca} was increased to 1.1, a change in the shape of the flux occurred, mainly in the z planes near the phantom surface. The greatest difference was observed when $n_{ca} = 1.4$, which was the n_{ca} closest to the phantom refractive index, when the matching of the refractive index was nearly ideal.



Figure 9 – MC simulation of photon flux in homogeneous phantom along plane y = 0 mm, when $h_{ca} = 3$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and 1.9. The dashed line represents the phantom top surface. For better visualization, logarithmic scale is used.

Source – By the author.

In figure 9, in which $h_{ca} = 3$ mm, we find that the widening of the flux distribution was greater than that observed in figure 8, and regions of minimum concerning the x-axis began to appear. To better visualize this effect, a contour plot analogue to figure 9 is presented in figure 10, where the black lines correspond to photon flux curves.



Figure 10 – MC simulation of photon flux in homogeneous phantom along plane y = 0 mm, when $h_{ca} = 3$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and 1.9. The dashed line represents the phantom top surface. Contour curves (black lines) are used for better follow the shape of a photon flux value. Source – By the author.

The differences in the photon flux distribution observed in figures 8 to 10 show that the illuminated volume changes when adding the CA on the phantom surface, and this change depends on both n_{ca} and h_{ca} . To compare this effect for the different simulation conditions, figure 11 presents the graphs of the $\log_{10} (flux) = -3$ curve, where it is possible to see that the lateral increase close to the surface occurs for all h_{ca} , but with minor changes in depth.



Figure 11 – Comparison of $\log_{10} (flux) = -3$ curves in homogeneous phantom for the different thicknesses and refractive indices of the simulated CA along plane y = 0 mm.

Source – By the author.

To better understand the difference that the CA causes in the simulated condition, we calculated the area within the photom flux curve for a each value of $\log_{10} (flux)$. Figure 12 illustrates the area taken in our calculations. For this, first, we calculated a binary matrix using the analyzed value as a threshold, the formula for this calculation is in the equation (3.1) where M is the resulting matrix and m_0 is the value of interest. Then, we made a sum of the values in this matrix and multiplied by the square of the resolution voxel (*fesc*), equation (3.2). In figure 13, we present the graphs of the area rate as a function of the analyzed I value.



Figure 12 – Scheme of the area (green region) under the $\log_{10} (flux)$ curves. Source – By the author.

$$M(x,z) = \begin{cases} 1, & \text{if } \log_{10} \left(flux \right) \le m_0 \\ 0, & \text{if } \log_{10} \left(flux \right) > m_0 \end{cases}$$
(3.1)

$$Area = \left[\sum_{x,z} M(x,z)\right] \times fesc^2$$
(3.2)



Figure 13 – Comparison between different h_{ca} of calculated areas of $\log_{10} (flux)$ curves normalized by the are when $n_{ca} = 1$. Each line in the graphs corresponds to a different value of n_{ca} . Values above the dashed line indicates an increase in the area when the CA was added. Source – By the author.

From figure 13, we can see that the CA layer, regardless the n_{ca} and h_{ca} , was able to increase the illuminated area by about twice the area when there is no CA ($n_{ca} = 1.0$), however, this increase happens for regions far from the light source where the $\log_{10} (flux) < 10^{-3}$. It is also possible to observe that for higher flux, the CA layer led to an even smaller illumination field (data points bellow the dashed line).

To evaluate the effect caused by different CA thicknesses and refractive indices, a graph of the area as a function of the refractive index for $\log_{10} (flux) = -3$ is presented in figure 14.

The dashed line indicates the value of the area when $n_{ca} = 1$, our control results, it means that below the line, we have combinations of n_{ca} and h_{ca} that leads to a smaller illuminated area, while above the line the combination that leads to a larger area.



Figure 14 – Comparison of the area as a function of n_{ca} for $\log_{10} (flux) = -3$ curve for $h_{ca} = 1, 2, 3$ and 4 in homogeneous phantom. The dashed line corresponds to the value of area when $n_{ca} = 1$.

Source – By the author.

In order to access possible changes relative to light propagation in-depth (z), in figure 15 we present a graph of the flux as a function of z for all simulated refractive index values when $h_{ca} = 3$ mm. Different from the changes observed in y or x directions, it is noticeable that there were no great flux variations in z regardless of n_{ca} variations.



Figure 15 – Photon flux as a function of depth (z) when $h_{ca} = 3$ mm, for all simulated n_{ca} in a homogeneous phantom.

As shown in the graphs of figure 10, the presence of CA on the phantom surface can lead to the appearance of maxima and minima in the photon flux curves. To understand this effect, in figure 16 we present the colormaps of the photon flux distribution along z = 5.5 mm plane (that is the first layer of the phantom), when $h_{ca} = 1$ mm for all n_{ca} values.



Figure 16 – MC simulation of photon flux in homogeneous phantom along plane z = 5.5 mm, when $h_{ca} = 1$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and 1.9. Source – By the author.



Figure 17 – MC simulation of photon flux in homogeneous phantom along plane z = 5.5 mm, when $h_{ca} = 4$ mm and $n_{ca} = 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8$ and 1.9. Source – By the author.

From the graphs of figure 16 it is possible to notice, for $n_{ca} > 1$, the existence of con-

centric rings with the center in the region of light source incidence, from the center to the edges of the maps, we see a flux decrease followed by an increase and then another decrease. A similar observation has been reported by FARREL²⁹ which experimentally demonstrated a prediction of the incompatibility of the CA refractive indexes based on the diffusion approximation of the RTE, however, he mentioned the limitation due to this approximation in regions close to the light source, which does not occur in this study, as we are working with a Monte Carlo RTE solution. One explanation for these rings' effect could be simply based on the total internal reflection (TIR) between the interfaces, a simple optical phenomenon with angular dependence that will be later addressed in our discussion.

Figure 17 shows photon flux maps of the first layer of the phantom for the largest h_{ca} simulated, 4 mm. Comparing figure 17 with figure 16 we can see that the location and "width" of the rings as a function of n_{ca} are different.

For a comparative analysis between the thickness and refractive index of the CA, the flux curves at z = 5.5 mm and y = 0 mm were plotted. For a comparative analysis between the h_{ca} and n_{ca} , the flux curves at z = 5.5 mm and y = 0 mm as a function of x were plotted. From these curves we compared the distance wring between two points (blue and black dots in figures 18 and 19) with the same flux value, one of them being determined as the point at the local maximum (black dot) of the curve. Figure 18 illustrates the procedure used to plot the curves and the location of the two points to determine w_{ring} . In figure 19 we have the graphs for different layers of CA and refractive indices with the blue and black dots locations for each curve. Figure 20 presents the graphs of w_{ring} as a function of h_{ca} .



Figure 18 – Schematics of the process used for determining the width (w_{ring}) , the distance between the blue and black dot.



Figure 19 – $\text{Log}_{10}(flux)$ as function of x position at y = 0 mm and z = 5.5 mm, for all h_{ca} simulated: (a) 1 mm, (b) 2 mm, (c) 3 mm and (d) 4 mm. Source – By the author.



Figure 20 – Rings width according to the CA thickness. Source – By the author.

With this analysis, it is possible to have an idea of equivalence between thickness and refractive indexes, because, for a given width (dashed line), it is noted that there are different conditions that generate it.

As already mentioned, to explain the existence of those rings, we can use a simple concept of geometric optics that is worth it to be reviewed in order to make this discussion clearer. Snell's law (equation (1.3)), which relates the change in the direction of light when there is a change of the medium. In figure 21a there is a schematic of light refraction, a light beam (red arrow) propagating from a medium 1 with refraction index n_1 arrives with an angle θ_1 at the interface with a medium 2 with refractive index n_2 ($n_2 > n_1$), which causes a deviation of the beam in medium 2 according to the equation (1.3), the Snell's law.



Figure 21 – Snell's law schematics showing: (a) light beam refraction when $n_2 > n_1$; (b) when $n_2 < n_1$, refraction occurs, but for angles of incidence larger that the critical angle (θ_c) , total internal reflection occurs.

In figure 21b we can observe a general behavior schematic depending on the angles to a medium in which n_1 is greater than n_2 . There is an angle in which the refraction will no longer happen and all light will be reflected, this is called a critical angle and is calculated by the equation (3.3). As can be seen, increasing the incidence angle θ_1 , the refracted beam angle will increase until reaching the limit $\theta_2 = \theta_c = 90^\circ$, from that the beams will not refract and will all be reflected, this phenomenon is called total internal reflection (TIR).

$$\theta_c = \arcsin \frac{n_2}{n_1} \tag{3.3}$$

Knowing this information, it was possible to calculate the θ_c for each interface of our phantom subject to TIR. The graph of critical angles as a function of simulated refractive indices can be seen in figure 22.



Figure 22 – Correlation between critical angle and n_{ca} at the interfaces present in the simulations. Red squares correspond to the interface between the CA and the air, blue circles correspond to the interface between the phantom and the CA, and the yellow triangles correspond to the interface between the CA and the phantom. The green line corresponds to the phantom refractive index. Source – By the author.

When a photon is travelling from the phantom to the CA, TIR is conditioned to the simulated n_{ph} , i.e., when $n_{ca} < n_{ph}$, there will be a θ_c (blue circles in figure 22). However, when a photon is travelling from the CA to the phantom, , there will be θ_c when $n_{ca} > n_{ph}$ (yellow triangles in figure 22). Thus, for analysis, we separated the regimes: less than and higher than n_{ph} . Looking at the first regime ($n_{ca} < n_{ph}$), we have that the critical angle of the upper interface declines, meaning that the closer the n_{ca} is to the n_{ph} , the more likely the photons will reflect on that interface and go back towards the phantom.

For the photons that are in the phantom and are scattered towards the CA, the critical angle increases for n_{ca} closer to n_{ph} , which makes them more likely to refract towards the CA, however, as they are most likely to reflect on the CA top surface, so they have a greater chance of returning to the phantom which in turn can undergo refraction and reflection.

Analyzing the second regime $(n_{ca} > n_{ph})$, in the phantom-CA interface the two phenomena will always happen, refraction and reflection. Whereas the CA-phantom interface will occur the TIR, since with the increase in n_{ca} there is a decrease in the critical angle which leads us to a higher probability of being reflected and since the CA-air interface also has a critical angle drop, this makes the photons that escaped from the phantom stay trapped in the CA.

3.4 Conclusion

Through these Monte Carlo simulations of light (at 630 nm) propagation in a homogeneous tissue optical phantom with human dermis optical properties, we were able to observe that adding a layer of coupling agent on the surface of the phantom will certainly change the propagation of the photons and this change is related to the thickness and refractive index of CA.

Monte Carlo simulations showed that a larger volume can be illuminated when a CA was used. The shape of photons propagation caused "light rings" to emerge under certain conditions of n_{ca} and h_{ca} . These "rings" seem to result from the TIR at the interface between CA and phantom.

4 TRANSPARENT LAYER OVER MULTI-LAYERED SKIN PHANTOM

In chapter 3, we showed that the light propagation within a homogeneous turbid phantom is changed due to the presence of a coupling agent (CA) placed on the phantom surface where the light beam is incident. It was observed that the changes depend on the thickness and the refractive index of the CA.

Besides the fact that a homogeneous phantom is good for method validation, it is well known that biological tissues are often composed of layers, and in this chapter we are going to use a multi-layered phantom, mimicking skin structure in order to have a more realistic environment for the MC simulations. We also investigated the effects of the tissue optical phantom roughness, and some features related to the light source, such as the angle of incidence and the possibility of using multiple sources.s

4.1 Simulated condition

4.1.1 Turbid medium

A multi-layered tissue phantom with skin-like optical properties was built based on parameters found in the literature. LaRochelle *et al.*³⁰ describe a skin model in which the layers optical properties are based on a work published by Meglinski & Matcher.³¹ This model had 6 layers: epidermis, papillary dermis, the dermis of the upper blood network, reticular dermis, the dermis of the deep blood network, and subcutaneous fat, as illustrated in figure 23. For our simulations, the stratum corneum layer was not considered, as shown in figure 24.³² In table 3 there are the optical properties of each layer of our simulated phantom when 630 nm light source is used.



Figure 23 – Skin tissue layers model. Source – ZHEREBTSOV.³²



Figure 24 – Schematics of the multi-layered skin phantom structure used in this chapter. Source – By the author.

Layer	$\mu_a(\mathrm{mm}^{-1})$	$\mu_s(\mathrm{mm}^{-1})$	g	n	Thickness (μm)
Epidermis	0.362517	11.1115	0.8	1.34	80
Papillary dermis	0.09492	8.8799	0.9	1.4	160
Dermis with superficial vascular plexus	0.50797	8.8799	0.95	1.39	80
Reticular dermis	0.08286	8.8799	0.8	1.4	1520
Dermis with deep vascular plexus	0.17957	8.8799	0.95	1.38	80
Hypodermis	0.09897	3.55196	0.75	1.44	8000

Table 3 – Skin optical proprieties used in the simulations.³⁰

Source – Adapted from LAROCHELLE. et al.³⁰

Above the surface of the epidermis, we added a layer of a coupling agent with a low absorption of $\mu_a = 10^{-5}$ mm⁻¹ and with no scattering effect. This layer had a thickness (h_{ca}) of 1.04, 2, 3.04 and 4 mm and refractive indices n_{ca} between 1.3 to 1.6 with a step of 0.1.

The total simulated volume was $(32 \times 32 \times 15.12) \text{ mm}^3$ and the skin phantom volume simulated was $(32 \times 32 \times 9.92) \text{ mm}^3$ with a voxel resolution of 80 μm^3 . This voxel resolution was chosen because it is the lower value that our GPU works correctly for these simulations since we have the limitation of the GPU RAM.

A MATLAB function (appendix B.1) was elaborated to create this volume, which takes as the parameter: the dimensions (voxel scale), CA thickness, and the matrix that represents the irregularities of the epidermis. It defined the distance in the z direction from the first layer of the volume (first air layer) to the first layer of the phantom (z = 5.2 mm), so that there was an empty space for varying the thickness of the CA layer.

4.1.2 Light source with normal incidence

For a more realistic simulation of light interaction with the skin, an irregular surface was created in the epidermis layer. To generate this irregular surface, a random matrix with values between 0 and 1 was generated and then a threshold was used to binarize, the final matrix is represented in figure 25, these 0 and 1 matrix elements represented a rough skin surface. When the CA layer was added, three possibilities were simulated: the CA fills the empty spaces (matrix elements = 0); the CA does not fill the empty spaces and in this case, we assumed that it was filled with air ($n_{ca} = 1$); and, the empty spaces were filled with medium with n close to "water" ($n_{ca} = 1.3$) and then the CA was added on the top of it. For comparison, epidermis with smooth surface was also simulated.



Figure 25 – Random matrix generated to simulate irregularities map of epidermis, the black color represent the air and white a epidermis.

Source – By the author.

The light source used was a "disk" type with a 0.48 mm radius placed in the medium center (0,0,0).

The number of photons simulated was 10^8 , as discussed in chapter 3, and all simulations were repeated 5 times to reduce noise. All conditions were executed through a single *script* (appendix B.2) with a loop for each executed condition. In table 4 setup variables used in the simulations are described.

Parmeters	Values	Description
cfg.unitinmm	0.08	Voxel resolution.
cfg.seed	1.6483e+09	Seed for the random number generator.
cfg.respin	5	Simulation repetition number.
cfg.nphoton	10^{8}	The total number of photons to be simulated.
cfg.isreflect	1	Consider refractive index mismatch.
cfg.isrefint	1	Consider refractive index mismatch.
cfg.isnormalized	1	Consider refractive index mismatch.
cfg.isspecular	1	Calculate specular reflection if source is outside.
cfg.outputtype	'flux'	Output is the fluence rate.
cfg.tstart	0	Starting time of the simulation.
cfg.tend	5e-9	Ending time of the simulation.
cfg.tstep	5e-9	Time-gate width of the simulation.
cfg.autopilot	1	Set automatically set threads and blocks in GPU.

Table 4 – General parameters used for simulations of multi-layered tissue phantom.

4.1.3 Light source with oblique incidence

As the angle of incidence plays an important role when light is traveling from a medium to another, due to the possibility of total internal reflection occurrence, a set of simulations was performed, in which the angle of incidence of the 'disk' beam was varied from 0° to 80° with steps of 10° . The position of the light source was displaced in such a way that the point of incidence at the skin-like phantom surface was always the same. For this, light source position was calculated using Snell's law and trigonometry, the formulas used are in the equation (4.1) and the schematic of figure 26 illustrates all the quantities involved in the calculations.

The script was used to do this simulation in appendix B.3.



Figure 26 – Schematics used to calculate the displacement of the light source required to position the beam in the center of the phantom surface.

Source – By the author.

$$dx = dx_1 + dx_2$$

$$dx_1 = dz_1 \tan \theta_i$$

$$dx_2 = \frac{\sin \theta_i dz_2}{\sqrt{n_{ca}^2 - \sin \theta_i^2}}$$
(4.1)

4.1.4 Multiple light sources

The examples presented so far were based on a single narrow light beam, however, most of the phototherapies are based on the application of light over a certain area. For this, there are several types of equipment and strategies to facilitate the photherapy procedure. It is possible to find commercial equipment based on an array of light sources distributed in a certain geometry; or, when the equipment has a single light source, the treatment strategy is to irradiate multiple points of the tissue to cover the target area.

Assuming that the therapeutic effect of both cases only depends on the total amount of light delivered to the tissue (J/cm²), the treatment can be performed using using either an equipment with multiple light sources or an equipment with a single light source but applied multiple times in a such a way that the distribution of the points has the same geometry of the multiple light sources of that first equipment, the expected result of both therapies would be the same.

We then performed simulations with and without the coupling agent in order to better understand how the dosimetry could be affected when we had the light being delivered to multiple points on the skin phantom surface. Thus, we proposed the use of a combination of four identical light sources (each source being a disk beam with 0.48 mm in radius) located at the vertices of a square. For this geometrical construction, each source was simulated separately and then the sum was taken.

In these simulations, it was used three distances of the center of the source relative to the medium's center (d): 0.48, 1.52, 2.48, and 3.52 mm. A view of the xy plane where the source's position is presented in figure 27 and the source coordinates for the different d are in the table 5. The script used in these simulations is in appendix B.4.

Source ID	d = 0.48 mm		d = 1.52 mm		d = 2.48 mm		d = 3.52 mm	
	x (mm)	y (mm)						
1	-0.40	0.56	-1.44	1.60	-2.40	2.56	-3.44	3.60
2	0.56	0.56	1.60	1.60	2.56	2.56	3.60	3.60
3	-0.40	-0.40	-1.44	-1.44	-2.40	-2.40	-3.44	-3.44
4	0.56	-0.40	1.60	-1.44	2.56	-2.40	3.60	-3.44

Table 5 – Coordinates of the different simulated sources.

Source – By the author.



Figure 27 – Schematics of the four sources (red dots) location in the xy plane. Source – By the author.

4.2 Results and discussion

4.2.1 Light source with normal incidence

The Monte Carlo simulation for the skin-like phantom with smooth epidermis is presented in figure 28, where the curves for photon flux are shown when $h_{ca} = 1.04$ mm for the different n_{ca} values. When the CA was added on the surface, we note that the shape of the curves changed in comparison with the map when $n_{ca} = 1$. The curves were distorted near the interface between the CA and the skin-like phantom, the lateral aperture of the curves increased. With more careful observation, it is possible to tell that this lateral aperture is less prominent for $n_{ca} = 1.5$ and 1.6 than for $n_{ca} = 1.3$ and 1.4, which are closer to the epidermis refractive index.



Figure 28 – MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane y=0 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$, 1.3, 1.4, 1.5 and 1.6. Contour curves (black lines) are used for better follow the shape of a photon flux value.

Source – By the author.

Some differences were observed for a thicker CA layer, $h_{ca} = 3.04$ mm. In figure 29 we can see the differences in the shape of the contour plot lines. As in figure 28, the curves were also distorted in comparison with the map for $n_{ca} = 1$. A larger lateral aperture was observed, however, the shape was completely different in some regions. If we look at the map for $n_{ca} = 1.4$ in figure 29, we see that at the line representing the surface of the epidermis, the flux did not simply decay with x distance from the point of incidence, but it did decrease, then increased and then decreased again.



Figure 29 – MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane y=0 mm, when $h_{ca} = 3.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6. Contour curves (black lines) are used for better follow the shape of a photon flux value.

Source – By the author.

With the results of figures 28 and 29 we can tell that the shape of the photon flux distribution within the skin-like phantom is affected by both the refractive index and thickness of the CA layer.

To better understand the differences caused by the variation of the refractive index, a curve was chosen and plotted in the same graph for a given CA thickness. In figure 30, the graphs $\log_{10} (flux) = -3$ curves are presented. It is now possible to see that for a certain thickness h_{ca} , the refractive index variation may cause a more or a less pronounced distortion of the shape of the photons' propagation. Nevertheless, the propagation along z for x = 0 mm seemed to be almost unchanged with variations in h_{ca} and n_{ca} .

Since the shape of the distribution changed in the sense of becoming wider near the interface between CA and skin-like phantom, we would like to know how much the illuminated volume of skin-like phantom could be changed by the different CA layer. Since we are considering a symmetrical photon flux distribution around the point of light incidence, we know that the area within the curves of figure 30 can be related to the illuminated volume. The area was then calculated and presented in figure 31 as a function of the refractive index.



Figure 30 – Comparison of $\log_{10} (flux) = -3$ curves in a multi-layered skin phantom with smooth epidermis for the different thicknesses and refractive indices of the simulated CA along plane y = 0 mm.

Source – By the author.



Figure 31 – Comparison of the area as a function of n_{ca} when $\log_{10} (flux) = -3$ for $h_{ca} = 1.04, 2.00, 3.04$ and 4.00 mm in multi-layered phantom with smooth epidermis. The dashed line corresponds to the value of area when $n_{ca} = 1$. Source – By the author.

In the graph of figure 31, the dashed line indicates the calculated area when $n_{ca} = 1$, i. e., no CA has been added. We can then see that using a CA led to an increase or a decrease in the area comprised by the $\log_{10} (flux) = -3$ contour line, and this result depends on the combination of n_{ca} and h_{ca} . The next step was to analyze the light distribution map in the epidermis since we observed the maximum and minimum flux regions. For this, graphs of the photon flux were made for the smooth epidermis and CA thicknesses of 1.04 and 3.04 mm, as can see in figures 32 and 33.



Figure 32 – MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane z=5.2 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$, 1.3, 1.4, 1.5 and 1.6. Source – By the author.

From figure 32, we can better see that the light flux was greatly affected by the CA layer with $h_{ca} = 1.04$ mm. At least in the most superficial layers of the skin phantom, the photons were able to propagate further in the x and y directions when the CA was placed than for $n_{ca} = 1$.



Figure 33 – MC simulation of photon flux in multi-layered skin phantom with smooth epidermis along plane z = 5.2 mm (epidermis layer), when $h_{ca} = 3.04$ mm and $n_{ca} = 1.0$, 1.3, 1.4, 1.5 and 1.6.

Source – By the author.

When h_{ca} was increased to 3.04 mm (figure 33), we also see photons propagation further when $n_{ca} \neq 1$. We can see that the pattern of flux distribution is different from that observed in figure 32 where we see that the color distribution goes from dark red (center) to blue (borders). When we look to the color map in figure 33 corresponding to $n_{ca} = 1.3$, we notice that the color distribution starts from dark red in the center to a green region, and then it becomes yellow again instead of changing to cyan. This ring pattern at the epidermis layer was also observed in the results of chapter 3. Later in this chapter, we will discuss the possible causes of these rings. In order to approximate to real skin, we created an irregular epidermis, as shown in figure 25. In figures 34 to 36, there is an intensity \log_{10} of flux on the xy plane for the epidermis layer when the $h_{ca} = 1.04$ mm for three conditions of CA contact with medium: the CA fills all the irregularities; the irregularities were filled with air; the irregularities are filled with a material with n = 1.3, which is close to the refractive index of water and the CA is on the top of this material.



Figure 34 – MC simulation of photon flux in multi-layered skin phantom with irregular epidermis filled with CA along plane z = 5.2 mm (epidermis layer), when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6.

Source – By the author.



Figure 35 – MC simulation of photon flux in multi-layered skin phantom with irregular epidermis filled with air and CA above along plane z=5.2 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6.

Source – By the author.



Figure 36 – MC simulation of photon flux in multi-layered skin phantom with irregular epidermis filled with water and CA above along plane z = 5.2 mm, when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0, 1.3, 1.4, 1.5$ and 1.6.

Comparing the photon flux of figures 34 to 36, it is possible to see that the simulation results were different for each configuration. Meaning that the matching of refractive index at the light incidence interface may play an important role. Looking at the case in which $n_{ca} = 1$, we note the irregularity of the light distribution. Now, looking specifically at the figure 34, we notice that with the addition of CA the distribution becomes more uniform. In figure 35, with the air between the CA and the skin phantom, there is an increase in photon flux, but it is possible to observe an irregular flux distribution. Finally, at figure 36, the distribution becomes visually a little more uniform, but comparing all situations, filling the irregularities with water was able to create the most uniform light distribution pattern. It may be indicative that the use of some material capable of filling imperfections is the best option.

To quantify how the addition of CA interferes with the homogeneity of light distribution, we used a statistical measure of the randomness that can be used to characterize the texture of an image, called entropy, to characterize the first layers of the skin phantom. In image processing, the entropy (H) is defined by equation (4.2).³³ In our case, we used local entropy that calculate the entropy in a 9-pixel neighborhood, and the calculated value was assigned to the central point. After calculating the local entropy, we made the integration of these values, thus getting a single value for each condition. It is important to note that the lower the entropy value, the more homogeneous the surface.

$$H = -\sum_{k} p_k \log_2\left(p_k\right) \tag{4.2}$$

The entropy for $h_{ca} = 1.04$ mm results corresponding to different layers of the skin phantom are presented in figures 37 to 39. Accessing the results at different layers is important because the epidermis, as already mentioned, is the source of heterogeneity. For this, we analyzed the entropies of the layers bellow the epidermis, as seen in the figures 38 and 39. Figure 37 shows the result for the epidermis (z = 5.2 mm), figure 38 shows the results for the first layer of the papillary dermis (z = 5.28 mm) and figure 39 shows the results for the second layer of the papillary dermis (z = 5.36 mm).

When analyzing entropy at the epidermis (figure 37), the first thing to note is that for rough surface and $n_{ca} = 1$, the value of entropy was the same, since they are equal conditions. When we look at $n_{ca} = 1.3$ we have that entropy for rough+CA and rough+water are close to the smooth surface, which shows us that the flux becomes more uniform within the skin phantom when a CA is placed on its surface. For $n_{ca} > 1.3$, rough+CA and rough+water is closer to the smooth surface.



Figure 37 – Comparison of the local entropy integration as function of n_{ca} for epidermis (z = 5.2 mm) for the different interface features evaluated.

Source – By the author.



Figure 38 – Comparison of the local entropy integration as function of n_{ca} for first layer of papillary dermis (z = 5.28 mm) for the different interface features evaluated. Source – By the author.

In figure 38 we have the entropy for the first layer of the papillary dermis, this is the first smooth layer beneath the heterogeneous epidermis. It is possible to observe that for $n_{ca} = 1$ the difference between the entropy for smooth and rough epidermis is smaller, and this difference remains for $n_{ca} = 1.3$. For $n_{ca} > 1.3$ we observe the same behavior of figure 37 but when $n_{ca} = 1.5$ the condition rough+CA becomes the closest to the smooth surface, and when $n_{ca} = 1.6$, rough+CA presents an entropy even smaller than that observed for the smooth epidermis.



Figure 39 – Comparison of the local entropy integration as function of n_{ca} for second layer of papillary dermis (z = 5.36 mm) for the different interface features evaluated. Source – By the author.

The entropy for the second layer of the papillary epidermis (at z = 5.36 mm) was also calculated, as can be seen in figure 39. It shows that for $n_{ca} = 1$ the difference between calculated entropy for smooth and rough epidermis is even smaller and it remains for $n_{ca} = 1.3$, whereas for rough+air this difference is greater. For $n_{ca} = 1.4$, we note that the value for rough+CA approximates the smooth value and becomes smaller for higher n_{ca} values.

Comparing figures 37 to 39, we can see that as the light propagates in depth (z) the effects caused by the irregularities become smaller and less important. We also observed that the rough+air condition is the one with the worst result concerning entropy, which shows that the use of a CA that fills the irregularities can make the skin optically more similar to a smooth surface.

After verifying the effect caused by the roughness, we returned to the smooth epidermis, and made the analysis to verify the flux gain or loss concerning our control in different layers of the phantom. For that, we took the flux map in xy in different z planes and normalized it by the flux in the control condition ($n_{ca} = 1.0$). In figures 40 to 43 for epidermis, we have the results of the logarithm in base 10 of that division. It is important to note that since we applied the logarithm scale, from every region where the value is greater than 0 (light blue contour), the CA caused a flux gain.



Figure 40 – Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis (z = 5.2 mm) when $h_{ca} = 1.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6.



Figure 41 – Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis (z = 5.2 mm) when $h_{ca} = 2.00$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6.

Source – By the author.



Figure 42 – Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis (z = 5.2 mm) when $h_{ca} = 3.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6.



Figure 43 – Ratio $(Flux/Flux_{air})$ contour map in a smooth epidermis (z = 5.2 mm) when $h_{ca} = 4.00$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6. Source – By the author.

Looking at these results for the epidermis layer (figures 40 to 43), first comparing the CA thickness, we observe that increasing h_{ca} , the area corresponding to the flux gain decreased, showing that a larger gain area occurred when $h_{ca} = 1.04$ mm (figure 40). Comparing the refractive indices, the higher the refractive index, the larger the flux gain region.

We also analyzed the first layer of hypodermis with this processing to understand the effects in depth. These results are in figures 44 to 47, where we see that the changes due to the CA thickness variation are similar to those observed in the epidermis layer, but when we look at the n_{ca} comparison as it increased, the area of flux gain decreased, and this gain was more evident when $n_{ca} = 1.3$



Figure 44 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer (z = 7.12 mm) when $h_{ca} = 1.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis is a smooth. Source – By the author.



Figure 45 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer (z = 7.12 mm) when $h_{ca} = 2.00$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis is a smooth. Source – By the author.



Figure 46 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer (z = 7.12 mm) when $h_{ca} = 3.04$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis is a smooth. Source – By the author.



Figure 47 – Ratio $(Flux/Flux_{air})$ contour map in in first hypodermis layer (z = 7.12 mm) when $h_{ca} = 4.00$ mm for $n_{ca} = 1.3$, 1.4, 1.5 and 1.6 and the epidermis is a smooth. Source – By the author.

Aiming to assess the photon flux penetration within the phantom, we extracted the data of flux as a function of depth (z) for different x positions: 0, 4, 8, and 12 mm. In figure 48 the results for $h_{ca} = 1.04$ mm are presented for a smooth epidermis surface.



Figure 48 – Flux decay as function of z for x = 0, 4, 8 and 12 mm and y = 0 mm with $h_{ca} = 1.04$ mm and smooth epidermis condition. Source – By the author.

In this sense, it is possible to see that the decay pattern varies with the x position. Thus, when moving away from the center of incidence, we observed the greater importance of the coupling medium presence. In the center (x = 0 mm), it is possible to observe a small increase in the first layers for the case without CA. However, as for the other x distances, the flux has a significant increase in the conditions with CA presence concerning the air. Looking at each situation, it is observed that for the investigated distance closer to the center (x = 4 mm), the

refractive index that optimizes the flux intensity is 1.5, and for other distances, the optimization occurred when $n_{ca} = 1.3$.

As already discussed in chapter 3, the main idea behind using a coupling agent is due to improving the matching of refractive indexes. To better understand all the details, it is necessary to add the concept of the reflection coefficient obtained from the Fresnel relations. In equation (4.3), there is a definition of the reflection coefficient $(R(\theta))$,³⁴ for the case in which the light propagates from medium 1 to 2, so θ_1 is the incidence angle, n_1 and n_2 are the refractive indices of the respective media and θ_c is the critical angle of the interface (equation (3.3)).

$$R(\theta_{1}) = \begin{cases} \frac{(n_{2} - n_{1})^{2}}{(n_{2} + n_{1})^{2}} & \text{if } \theta_{1} = 0\\ \frac{1}{2} \left[\frac{\sin^{2}(\theta_{1} - \theta_{2})}{\sin^{2}(\theta_{1} + \theta_{2})} + \frac{\tan^{2}(\theta_{1} - \theta_{2})}{\tan^{2}(\theta_{1} + \theta_{2})} \right] & \text{if } 0 < \theta_{1} < \theta_{c} \\ 1 & \text{if } \theta_{c} \le \theta_{1} < \frac{\pi}{2} \end{cases}$$
(4.3)

It is important to note that the reflection coefficient shows the percentage of the photon probability that arrives at a certain angle to be reflected or refracted at that interface, so when R = 0 there is no probability of it being reflected, then it is refracted, and when R = 1 there is a 100% chance that the photon will be reflected at that interface, leading to the total reflection. Using equation (4.3), we plot the reflection coefficient as a function of the incidence angle for all interfaces in the multi-layer tissue phantom, figure 49. Because of the multiple photon scattering events in the medium, there can be photons arriving from all directions at the interface, so the smaller the incidence angle with a higher probability of being reflected, the greater the chance of the photons remaining in that medium.



Figure 49 – Reflection coefficient as a function of the incidence angle for the multi-layered skin phantom, (a) in the light incidence direction and (b) in the oposite direction, at each interface of the skin phantom.

From figure 49, it is possible to see that there is a higher probability for the photons to be reflected from reticular demis to dermis with deep vascular plexus (figure 49a) and from hypodermis to dermis with deep vascular plexus or papillary dermis to epidermis (figure 49b). These differences in the Fresnel coefficients show the importance of using muti-layered skin phantom and not a homogenous phantom when studing light propagation theoretically or *in vitro*.

Figure 50 shows $R(\theta_i)$ as a function of θ_i for different n_{ca} at each interface with the CA: Epidermis-CA(figure 50a), CA-Epidermis (figure 50b) and CA-Air (figure 50c).



Figure 50 – Reflection coefficient with incidence angle for the n_{ca} simulated, in (a) CAepidermis direction, in (b) epidermis-CA and (c) CA-air. Source – By the author.

From figure 50a we can see two groups of curves: one for n_{ca} from 1 to 1.3 and the second for n_{ca} from 1.4 to 1.6. In the first group, the curves grow faster than the second group; it means that the photons travelling back from the epidermis have a higher probability of being

reflected at the CA interface. The first group also corresponds to the cases where there is a critical angle (since the refractive index of the epidermis is greater) that may lead to total internal reflection.

Figure 50b also shows this two groups feature, but the faster group correspond to $n_{ca} =$ 1.6, 1.5 and 1.4, meaning that the photons travelling from the CA have higher probability of being reflected at epidermis interface. When we look at figure 50c, we do not see two groups; all curves have similar shapes and the probability of the photons travelling from CA to the air being reflected at the interface is higher as greater the n_{ca} .

4.2.2 Light source with oblique incidence

The physical phenomena responsible for the effect caused by CA are the refraction and reflection, thus the variation of the angle of incidence may lead us to interesting results. In figure 51 we have the results for a control condition (air) for different incidence angles. As we can see, when the light beam has oblique incidence, the spot shape and size change at the phantom surface. It means that despite the photon flux is the same, the photon density changes, in our case, it decreases as the beam size increases.



Figure 51 – MC simulation of photon flux in multi-layered skin phantom along plane y = 0mm for different incidence angle, when $h_{ca} = 1$ mm for $n_{ca} = 1.0$. Source – By the author.

Figure 52 shows the results for $n_{ca} = 1.3$ and $h_{ca} = 1.04$ mm. It is possible to note the refraction. The behavior for θ_i increase is similar to the one without CA condition, the area of the light spot in epidermis is greater for high θ_i , but the intensity is lower than that for normal incidence.


Figure 52 – MC simulation of photon flux in multi-layered skin phantom along plane y = 0mm for different incidence angle, when $h_{ca} = 1$ mm for $n_{ca} = 1.3$. Source – By the author.

In order to better access the effects previously mentioned caused by the variation of θ_i , the 0.3 flux curves (i.e., the curve when the flux was 30% from the initial value) were plotted together and the results for without CA and $n_{ca} = 1.3$ are in figure 53. We observed that the incidence angle variation caused a significant difference in the shape of light distribution within the skin phantom both for $n_{ca} = 1$ and $n_{ca} = 1.3$. A careful comparison between figure 53 shows that, the light travelled a little deeper when a CA with n = 1 was used.



Figure 53 – Comparison of Flux = 0.3 curve inside the multi-layered skin phantom along y = 0 mm plane for different indices angles. The top graph is the air condition and bellow is $n_{ca} = 1.3$.

Source – By the author.

We also made an analysis of the maximum depth (Δz) and the epidermis width (Δx) as a function of the incidence angle, the process used are better described in figure 54 and the results are presented in figure 55. It was made to better visualize the differences between the control (air) and $n_{ca} = 1.3$. The graph in figure 55 shows that regardless the refractive index of the CA, the penetration depth decreases as the incidence angle increases; however, for the width, the increase was observed as the angle of incidence increased. We can also observe that for a certain angle, a small decrease in depth was observed when *n* increases.



Figure 54 – Schematics of the procedure used to calculate Δz and Δx . Source – By the author.



Figure 55 – Δz (left axis) and Δx in the epidermis (right axis) as function of incidence angle for flux=0.3 when $h_{ca} = 1.04$ mm. Source – By the author.

It was possible to observe that the use of a coupling agent on the top surface of the phantom did not promote any evident improvement for an oblique incidence of light.

4.2.3 Multiple light sources

As an example of multiple sources, we explored the situation where we have 4 disk-type sources, each source with a radius of 0.48 mm. The sources were distributed at the vertices of a square, at the positions described in table 5, and their photon flux maps at the top surface of the volume simulated (z = 0 mm) is presented in figures 56 and 57. To better visualize differences between one and four sources, figure 56 shows the graphs for each source separately and figure 57 the sources addition.



Figure 56 – MC simulations of photon flux in multi-layered skin phantom along plane z = 0mm for each source used to compose the array when d = 0.48 mm. Source – By the author.



Figure 57 – MC simulations of photon flux in multi-layered skin phantom along plane z = 0 mm for light sources sum when d = 0.48 mm.

Source – By the author.

To start the analysis of the effect of the source composition with CA addition, figure 58 shows the contour plots of the photon flux at z = 5.2 mm (epidermis layer) for the case when $h_{ca} = 1.04$ mm.

If we compare the Monte Carlo simulations for $n_{ca} = 1$ in figure 58, we notice the effect of the sum of the light fields. Considering, for example, the curve in which $\log_{10} (flux) = -1$ (orange area) it is possible to observe that when d = 1.52 mm, the orange area is wider, however, there is a small region in the center (greenish), where the flux is lower, which can become a problem if the target is at that region. Comparing the effect caused by the CA in figure 58, it is observed that the best effect, regardless of the distance between the sources, is caused by the use of a CA with $n_{ca} = 1.3$, which is closest to the epidermis refractive index, that is the layer analyzing in this graphs. It is worth noting that the most intense curves (greater than $\log_{10} (flux) = -2$) have their area reduced with the use of CA, but the least intense curves (lower than $\log_{10} (flux) = -3$) can reach further distances.



Figure 58 – MC simulations of photon flux in multi-layered skin phantom along z = 5.2 mm (epidermis layer) when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$, 1.3, 1.4, 1.5 and 1.6. Source – By the author.

To understand what happens at different depths, in figures 59 and 60, we have the photon flux contour graphs for the beginning of each layer that makes up our phantom, for $n_{ca} = 1.0$ and $n_{ca} = 1.3$.



Figure 59 – MC simulations of photon flux in multi-layered skin phantom along each skin layer simulate when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$. Source – By the author.

Observing the figure 59, we see that at deeper layers (figure 59a), the sum of the four sources ends up approaching the profile of a single source, this behavior eventually disappears when we use the most separate sources (figures 59b and 59c), where even at deeper layers, it is

possible to discriminate each of the four sources. We also see that for z = 7.12 mm (first layer of hypodermis), the curves for $\log_{10} (flux) < -2$ have similar area, for $\log_{10} (flux) = -2$ has an increase to d > 0.48 mm but with its increase a lower flux appears in the central region. This effect was observed in the epidermis with greater intensity.



Figure 60 – MC simulations of photon flux in multi-layered skin phantom along each skin layer simulate when $h_{ca} = 1.04$ mm and $n_{ca} = 1.0$. Source – By the author.

Comparing the results without CA (figure 59) and the case at $n_{ca} = 1.3$ (figure 60), we have that in the first layers from $\log_{10} (flux) = -3$ there is an increase in the area, however when we looking at the hypodermis an area increase is observed only from the curve $\log_{10}\left(flux\right) = -4.$

Photon flux as a function of z, at x = 0 mm and y = 0 mm for the different refractive index were analyzed for $h_{ca} = 1.04$, as shown in the figure 61. For d = 0.48 mm and d = 1.52mm (figures 61a and 61b) we see that the curves for $n_{ca} = 1$, i.e, without CA, are higher than for the other n_{ca} values (with the presence of CA).For a greater distance between the sources (figures 61c and 61d), the curve for $n_{ca} = 1$ was lower than the other curves. These observations show us that under certain conditions, n_{ca} combined to d was capable of changing the light penetration profile within the skin phantom.



Figure 61 – Photon flux as function of z at x = 0 mm and y = 0 mm when $h_{ca} = 1.04$ mm in (a) d = 0.48 mm, (b) d = 1.52 mm, (c) d = 2.48 mm, (d) d = 3.52 mm Source – By the author.

In the results presented so far, we have used 1d and 2d views, to better illustrate the entire volume illuminated on the surface for $\log_{10} (flux) = -3$, as seen in figure 62.



Figure 62 – Surface plot of $\log_{10} (flux) = -3$ for the different distances d, comparing all n_{ca} simulated.

Source – By the author.

We can see from these 3D plots that the CA caused a change in light distribution shape. Now comparing the volumes for the different distances, when the sources are closer, d = 0.48 mm (figure 62a), the analyzed curves approach the case in which there is only one source. When d = 1.52 mm (figure 62b) it is still possible to observe a limit in which the surface approaches a single source with a greater area, however, for d = 2.48 mm and d = 3.52 mm, this effect no longer occurred. When the CA was present, we observed that for all distances between the sources the largest $\log_{10} (flux) = -3$ volume was observed when $n_{ca} = 1.3$.

4.3 Conclusions

In this chapter, we observed the effect of a CA placed on the top surface of a skin-like multi-layered phantom in different conditions: normal incidence in a medium with a smooth interface and with an irregular interface; oblique incidence with a smooth interface; and finally a combination of 4 sources on a smooth interface.

Comparing the Monte Carlo simulations with CA and without (figures 40 to 47), we verified that the combination of $n_{ca} = 1.3$ e $h_{ca} = 1.04$ mm resulted in a larger field of illumination concerning all 3 dimensions of propagation. Analyzing the effect of CA on an irregular surface, the calculation of local entropy showed a greater uniformity when $n_{ca} > 1$, which is a significant result since irregularities are commonly found on the biological tissue surface. It shows the importance of looking to the cause of the CA effect: matching of refractive indices. Thus, when we look at the refractive index, we see that $n_{ca} = 1.3$ is the closest to the epidermis index.

The section 4.2.2 evaluated the CA effect caused when using a light source with oblique incidence. When the angle of incidence was varied, the geometry of the light spot at the CA surface also changed (the greater the angle, the greater the light spot) and this is certainly the main cause for the observed changes in the shape to light distribution. A careful comparison between the MC simulations with CA and without CA (figure 53) showed that the light travelled a little deeper without CA ($n_{ca} = 1$).

Analyzing the simulations for multiple light sources (section 4.2.3) in different positions, we noticed that the presence of the CA causes homogenization of these photon flux curves shapes making them similar to a field from a single source with greater area. We observed that for all simulated distances between the sources, the largest $\log_{10} (flux) = -3$ volume was observed when $n_{ca} = 1.3$ and $h_{ca} = 1.04$ mm.

5 A MIRROR-LIKE OBJECT OVER MULTI-LAYERED SKIN PHANTOM

It is not difficult to find situations where the light is not directly delivered to the tissue but is delivered through a metallic handheld probe. Thinking about these situations, in this chapter, we are going to simulate the effects caused by a mirror-like object placed on the top surface of a skin phantom. For this, we added a disk with optical properties like a mirror around the source and evaluated how radius variation affects light distribution. To measure this variation, we used two detectors, one beside the source and another inside the phantom in the same xy position of the source.

5.1 Simulated conditions

In order to simulate the effects caused by a highly reflective material placed on the top surface of a skin phantom, we had to establish the best optical parameters that would create a mirror-like object. We varied the refractive index to find the best value which would cause total reflection. For this, we created a simple setup: an air layer and a 1.25 mm thick reflective material inside the air, the total volume was $(60 \times 60 \times 5)$ mm³, with 0.25 mm resolution. The optical properties used for the simulations are in table 6. The light source was a cone-beam with 0.9 radians half-angle to better visualize the reflected photons.



Figure 63 – Schematics of the simulation setup used for reflective material optical properties validation.

Source – By the author.

Medium	$\mu_a(mm^{-1})$	$\mu_s(mm^{-1})$	g	n
Air	10^{-5}	0	1	1
Reflective material	10^{-5}	1	-1	10^x , $x = 2, 3, 4, 5, 6$ and 7
	Sour	a By the out	hor	

Table 6	5 – (Optical	prop	erties	used	in	the	simul	lations.
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Source – By the author.

After establishing the optimum condition for the refractive index, we implemented a medium similar to that described in the section 4.1.1, and above the surface, a reflective cylinder with a 2.5 mm height and different radius was placed concentric to the light source, the disc radius (r_m) was varied from 0.48 to 3.12 with a 0.24 mm step. Two detectors were located in different positions to measure the the number of photons arriving at their positions. One detector was located next to the source at (x, y, z) = (0.32, 0, 31.25) mm (detector 1) and the other below the source at the end of dermis layer at (x, y, z) = (0, 0, 4.42) mm (detector 2), as shown in figure 64. The detectors were implemented with geometry similar to "optical fiber probe tips", for this, very narrow empty cylinders were created ($80\mu m$ diameter) in order to locate the detectors.

Since the detector may disturb the system, MC simulations were also performed without the detectors for comparison. In this case, the light source was a disk with an 80 μm radius, as well as the detectors.



Figure 64 – Schematics of the simulation setup for the reflective material simulations. Source – By the author.

All simulations parameters were the same as mentioned in chapter 4 and presented in table 4.

5.2 Results and discussion

Figure 65 shows the MC simulations for six different values of refractive index used to determine the best optical properties that could generate the mirror effect. One can see that the higher the n, less photons can pass through the material. When $n = 10^5$, no photons were detected within the turbid medium and we observed no difference when comparing with higher tested n. We then assumed the refractive index for the reflective material (n_{ref}) as the value of 10^6 in the following simulations.



Figure 65 – Monte Carlo simulation for validation of total reflective material. The white lines correspond to reflective material interfaces

Source – By the author.

In figure 66 we have the maps of flux distribution along y = 0 mm plane, when the simulations were performed without the detectors, without reflective material (control situation), $r_m = 0.48$ mm and $r_m = 3.12$ mm.



Figure 66 – MC simulations of photon flux in multi-layered skin phantom for the conditions: without reflective material, $r_m = 0.48$ mm and $r_m = 3.12$ mm. Source – By the author.

A careful observation of figure 66 shows us that the largest reflective material caused an increase in the light penetration: the cyan color region when the $r_m = 3.12$ mm went further than the other simulated conditions. To better visualize these differences, figure 67 shows the different curves ($\log_{10} (flux) = -3$ to 1 with 0.5 steps) for the control and all reflective radius.



Figure 67 – Comparison of the logarithm scale photons flux curves for the values -3 to 1 with 0.5 variation for all reflective radius analyzed. Source – By the author.

From figure 67, it is possible to observe that for higher intensities there are no major changes, however, as the intensity flux decreases, the reflective material caused more pronounced changes, increasing the volume within a certain flux.

The next step was to analyze the simulations with the detectors, to quantify the number of photons detected by each detector. The number of photons detected as a function of the radius of the reflective material is presented in the graph of figure 68. The total number of simulated photons was 10^8 .



Figure 68 – Comparison of number of photons detected by detectors 1 and 2 as function of the reflective radius.

Source – By the author.

As expected, the number of detected photons was greater for detector 1, since it was much closer to the light source than detector 2. The curves show that as the radius of the reflective material increased, the number of photons also increased for both detectors. This result is likely related to the fact that with a larger reflective material the back-scattered photons traveling beneath the disk will be reflected back to the phantom and continue to propagate.

To assess how different the increase of the number of detected photons was for detector 1 or detector 2 the percentage rate of increase relative to a control condition (without the reflective material) was obtained, as shown in figure 69.



Figure 69 – Rate of increase in the number of photons detected with respect to control versus the reflective radius.

Source – By the author.

With the data of the percentage of increase, we can notice that the detectors have similar behavior, being that for smaller radius the increase for detector 1 is greater and for the larger radius detector 2 has a greater increase. The percentage of this increase varies from 5% to approximately 26%. It is also possible to visualize that the rate of increase is higher for detector 1 than 2. This result shows that the effect caused laterally in the most superficial layers may be greater than the effect caused in-depth since detector 1 is on the surface and 2 at the epidermis.

5.3 Conclusions

From checking different settings, it was possible to determine the optical properties $(\mu_a = 10^{-5} \text{ mm}^{-1}, \mu_s = 1 \text{ mm}^{-1}, g = -1 \text{ and } n = 10^5)$ that produce an effect similar to a mirror, reflecting all the incoming light.

The MC simulations with the presence of a reflective medium showed a change in the light distribution, showing an increase in the number of photons detected. This increase was higher the larger the radius of the reflective material (r_m) .

6 FINAL CONSIDERATIONS AND CONCLUSIONS

6.1 Final considerations

In the present thesis, we have implemented, tested and presented good results of Monte Carlo simulations when a layer of a transparent material is placed on the skin surface during a biomedical optics procedure with a 630 nm light source.

The importance of a study like this relies on the fact that light dosimetry for phototherapies, photodynamic therapy, or photodiagnostics is mostly based on empirical data reported by literature, even though the optical properties of the skin, as well as other tissues, can be different from patient to patient or from site to site. Moreover, it is not difficult to find situations in which a certain transparent material is between the skin and the light source, like a glass window at the output tip of a laser probe, or a thin plastic film used as a sanitary barrier between the light device and the patient's skin.

Despite being a simple approximation, the use of a homogeneous turbid phantom, as Intralipid, is often reported in the literature as a simulation medium for biological tissues.³⁵ In this thesis, we started the MC simulations in chapter 3 using a homogenous turbid phantom (with optical properties similar to the dermis) to access the light distribution when a transparent material was placed on the top surface of the turbid phantom.

As the skin is the most external barrier of the human body and is the biological tissue that first receives the photons during a biomedical optics procedure, in chapter 4 we implemented a more complex and realistic multi-layered skin phantom, in which the optical properties and thickness of each skin layer were defined.

Comparing the analogous results of chapters 3 and 4, from figure 70 we can clearly see differences in the light distribution. In the multi-layered skin phantom the photons were able to propagate further than in the homogeneous phantom, due to the differences in the optical properties of the phantoms. The optical properties of the homogeneous phantom were set as the dermis, while the multi-layered phantom has different optical properties for each layer, being the hypodermis the thickest layer of the phantom. The hypodermis is the skin layer with the lowest μ_s and also a low μ_a , hence allowing the photons to propagate to further depths.



Figure 70 – MC simulation of photon flux along plane y=0 mm without CA. In (a) is the homogeneous phantom and in (b) a multi-layered skin phantom. Source – By the author.

These results show us that phantom structures, as well as their optical properties, highly influence the propagation of the light through a phantom, and how relevant is to consider a more realistic phantom when small changes are significant for the study.

Besides the multi-layer aspect of the phantom, its surface features can also play an important role and it was accessed in section 3.3 when we compared smooth (figure 33) and rough surfaces (figure 34). This analysis is important because it is known that a rough surface could cause an increase in diffuse reflectance.³⁶

This comparison showed us that when the surface is smooth, the color map of the light distribution at the phantom surface is more uniform, while for the rough surface, the color map is more "noisy". Moreover, we observed that using a transparent material over the rough surface was able to diminish the "noise" leading to more uniform light distribution, more similar to that obtained for a smooth surface. This effect had already been observed in a previous experimental study by our group,^{24,37} in which carbopol gel was placed over the irregular surface of a homogenous solid phantom leading to a more uniform light distribution profile within the solid phantom. Therefore, with the MC simulations carried out, we complement this analysis, since now we access the light distribution in the entire studied medium and observe the effects in more detail.

Another important parameter that must be taken into account is the angle of light incidence. In section 4.2.2 we presented the results of MC simulation showing that an oblique incidence changes the shape and size of the light beam spot, which will certainly change the shape of the light propagation within the tissue, which in turn will affect the light dosimetry.

Thinking about light dosimetry, we may ask "What are the implications of using a CA in a phototherapy procedure?". To answer this question we have to look carefully at the outcomes of our MC simulations. According to our results, we may say that using a CA with a particular refractive index and thickness it is possible to change the spatial light distribution within the skin, and then it can be strategically used aiming for a more uniform illumination during phototherapies. In phototherapies, a laser source with a narrow beam is often used in multiple points on the skin to deliver the intended light fluence. The distance between the points are always a subjective parameter and simulations like the ones presented in this thesis (section 4.2.3) may help to determine the optimal distance between the points, besides recommending the use of a thin layer of water, for instance, for matching of refractive index to have an even more uniform field of illumination.

As one can see, several parameters may influence the light dosimetry, and our last investigation of this thesis was based on the use of a mirror-like material over the skin phantom in order to observe how a highly reflective material could affect the light propagation within the phantom. Our simulations showed (section 5.2) that when the mirror-like object is used, an effect similar to that seen with the CA happens, however in greater proportions. In this case, the mirror-like object avoids the underneath back-scattered photons to escape from the phantom surface; these photons are reflected at the 'mirror' interface back to the phantom and continue to propagate.

This investigation can be relevant when we consider the fact that some devices built for biomedical optics applications have a metallic piece surrounding the light source and which can be in contact with the tissue during the application. One example of this type of device is the one that conjugates low-level laser therapy and ultrasound therapy used by our group to treat patients with fibromyalgia.³⁸ The SMA connector used in the optical fibers end tip is commonly present during the data acquisition in photodiagnostics techniques, and this is another example of a metallic (highly reflective material) piece that may influence the light propagation in the tissue.

Since 1989, MC simulations have been used to study photon migration in biological tissues.⁷ At first, due to computational limitations, MC simulations were very time consuming, taking several hours or even days to get the results. With technological development, it was expected that MC simulation would turn into a more feasible tool in the seek for a real-time dosimetric tool.

Accelerated methods such as the one used in this thesis, the Monte Carlo eXtreme, allow us to get the simulation results in a few minutes. The use of MC for photon transport has already been widely used in various applications such as light dosimetry for photobiomodulation,^{39,40} simulation of photodynamic therapy,^{30,41–44} and use for modeling diagnostic techniques.⁴⁵ Although several studies showing the validity of the use of MC simulations to study light propagation in biological tissues,^{12,46} it is important to note that MC does not replace an experimental study. However, it certainly helps in planning an experiment since it allows to make several tests observing small theoretical aspects that are often not possible in an experiment.

6.2 Conclusions

In conclusion, this thesis showed us that:

- The presence of a CA over a homogeneous or multi-layered phantom can change the light propagation within the phantom;
- The composition of the CA (refractive index) and its quantity (thickness) plays an important role in the changes in light propagation;
- A CA with a refractive index of around 1.3 (e.g., water) seems to be the best option when we want to produce the largest illumination field;
- The CA is able to create a more uniform light distribution within the phantom with a rough surface, making it more similar to a smooth surface phantom;
- When the angle of incidence of the light beam is changed, the beam spot geometry also changes and this changes the shape of the light propagation;
- When multiple light sources or multiple points of light application are used, it is possible to find a combination of CA and distance between the sources/points that will produce a more uniform light distribution, which will be similar to the light distribution generated by a larger light beam;
- A mirror-like object placed on the surface of the skin phantom is able to increase the number of detected photons and this increase is higher as higher the mirror-like object;
- MCX has proven to be a valuable tool towards a better understanding on the light propagation in biological tissues according to different irradiation strategies. It can also help to path the way to the personalization of light dosimetry in the clinics.

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APPENDIX

APPENDIX A – CHAPTER 3 SCRIPTS

A.1 Main code

```
1 clear; close all; clc;
2 addpath(pwd)
3 file = 'homogeneo/matfile';
4 cd(file);
5
6 % simulation setup
7 f_esc=0.25;
8 x=1:32/f_esc;
9 y=1:32/f_esc;
10 z=1:15.5/f_esc;
11
12 numbersim=1;
13 font_position = [size(x, 2)/2, size(y, 2)/2, 0];
14
15 s font=2;
16 prop_medium = [0.27 18.7 0.81 1.41];
17 n_photon = 10^{8};
  n = [1 \ 1.1 \ 1.2 \ 1.3 \ 1.4 \ 1.5 \ 1.6 \ 1.7 \ 1.8 \ 1.9];
18
19
  88 loop
20
  for s_coup = 1:4
21
22
       s_coup = s_coup/f_esc;
23
       f_coup = round(5.5/f_esc);
24
       i_coup = f_coup-s_coup;
25
26
       vol=ones(size(x, 2), size(y, 2), size(z, 2));
27
       vol(:, :, i_coup:f_coup) = 2;
28
       vol(:, :, f_coup+1:end) = 3;
29
30
       name=['var_n_camada' num2str(s_coup) '_sim'
31
        \rightarrow num2str(numbersim)];
       disp(name)
32
33
```

```
for i=1:size(n,2)
34
           prop_coup=[10e-6 0 1 n(i)];
35
36
           %% execution
37
           [fcw2,f2,cfg,t2(i)]=exe_sim(prop_coup, f_esc,
38

→ prop_medium, vol, font_position, s_font,

→ n_photon, name);

39
           %% save results
40
           save([name '_n_' num2str(n(i)*100) '.mat'],
41
           42
       %% log file
43
44
          fileID = fopen([name '.dat'], 'w');
45
          fprintf(fileID, 'Resolution:%.2f mm\r\n', f_esc);
46
          fprintf(fileID, 'Vol size\r\nx:%d\t y:%d\t z:%d
47
          \rightarrow \r\n', size(x, 2), size(y, 2), size(z, 2));
          fprintf(fileID, 'h_ca:%d\t Inicio:%d\t Fim:%d\r\n',
48

    s_coup, i_coup, f_coup);

          fprintf(fileID, 'CA optical prop.\r\n');
49
          fprintf(fileID, 'mua: %.5f\t mus: %.5f\t g:%.3f
50
          \rightarrow n=', prop_coup(1), prop_coup(2), prop_coup(3));
          fprintf(fileID, '%.2f', n);
51
52
          fprintf(fileID, '\r\n Phantom optical prop.\r\n');
53
          fprintf(fileID, 'mua: %.5f\t mus: %.5f\t g:%.3f
54
          \rightarrow n=%.2f\r\n', prop_medium(1), prop_medium(2),
          \rightarrow prop_medium(3), prop_medium(4));
          fprintf(fileID, 'Source Position (x,y,z):');
55
          fprintf(fileID, '%d ', font_position');
56
          fprintf(fileID, '\t Source width:%.2f\r\nn
57

→ photons:%d', s_font, n_photon);

58
59
          fclose(fileID);
60
          T = table(n', t2', 'VariableNames', {'n' 't2'});
61
          writetable(T,[name '_timeexec.dat'],
62
```

63 **end**

64 **end**

A.2 Simulation execution

```
1 function [fcw2, f2, cfg, t2] = exe_sim(prop_coupling,
      f_esc, prop_medium, vol, font_position, size_font,
    \hookrightarrow
      n_photon, name)
   \hookrightarrow
2
3
     setup parameters
       cfg.seed=[hex2dec('623F9A9E')];
4
       cfg.nphoton=n_photon;
5
       cfg.session=name;
6
7
     %% volume
8
       cfg.vol=uint8(vol);
9
       cfg.unitinmm=f_esc;
10
11
         optical propieties
     12
     cfg.prop=[0 0 1 1;
13
       10e-6 0 1 1;
14
       prop_coupling;
15
       prop_medium];
16
     %% Source
17
       cfg.srcpos=font_position;
18
       cfg.srcdir=[0 0 1];
19
       cfg.srctype='disk';
20
       cfg.srcparam1=[size_font 0 0 0];
21
     %% temporal parameters
22
       cfg.tstart=0;
23
       cfg.tend=5e-9;
24
       cfg.tstep=5e-9;
25
26
     %% GPU thread configuration
27
       cfg.autopilot=1;
28
       cfg.gpuid=1;
29
30
     %% Simulation
31
32
```

33		<pre>cfg.isreflect=1; % enable reflection at exterior</pre>
		\leftrightarrow boundary
34		cfg.isrefint=1; % enable reflection at interior
		\leftrightarrow boundary too
35		cfg.isspecular=1;
36		cfg.issrcfrom0=0;
37		cfg.isnormalized=1;
38		cfg.outputtype='flux';
39		
40		tic;
41		[f2]=mcxlab(cfg);
42		<pre>fcw2=f2.data*cfg.tstep;</pre>
43		t2=toc;
44	end	

APPENDIX B – CHAPTER 4 SCRIPTS

B.1 Creating the simulated volume

```
1 function [v, i_coup] = create_vol(x, y, z, f, s_coup,
   \hookrightarrow
      m_rand)
       %x,y,z,s_coup em mm
2
       z = 18.4 \text{ mm tissue } +5.2 \text{ mm}
3
       %Conversion from mm to voxel
4
       X = 1: (x/f);
5
       Y = 1: (y/f);
6
7
       Z = 1: (z/f);
       i_t = 5.2/f;
8
       s_coup = round(s_coup/f);
9
       %Thickness calculation
10
       i_coup = i_tec-s_coup;
11
       s(1) = round(0.08/f);%Epidermis
12
       s(2) = round(0.160/f); %Papillary dermis
13
       s(3) = round(0.08/f); %Dermis with superficial vascular
14
       ↔ network
       s(4) = round(1.52/f);%Reticular dermis
15
       s(5) = round(0.08/f); %Dermis with deep vascular
16
       ↔ network
       s(6) = round(8/f);%Hypodermis
17
       % Positions
18
       p = 0;
19
       for i = 1:size(s, 2)
20
           if i = = 1
21
               p(i) = i_{tec+s(1)};
22
           else
23
                p(i) = p(i-1) + s(i);
24
           end
25
       end
26
       % volume
27
       v = uint8(zeros(size(X, 2), size(Y, 2), size(Z, 2)))
28
        v(:, :, 1:(i_tec-1-S_coup)) = 1;
29
       v(:, :, (i_tec-1-S_coup+1):i_tec-1) = 2;
30
```

```
for i = 1:size(s, 2)
31
32
            if i == 1
                v(:, :, p(i)-1) = m_rand+3;
33
            else
34
                v(:, :, p(i-1):(p(i)-1)) = 3+i;
35
            end
36
       end
37
   end
38
```

B.2 Simulation script for a normal incidence

```
1 close all;clear;clc;
2 %% axis
3 x=32; %mm
4 y=32; %mm
5 z=15.04; %mm
6 f=0.08; %voxel = 80 microns
7 cfg.unitinmm = f;
8 X=1:(x/f);
9 Y=1: (y/f);
10 Z=1:(z/f);
11
12 %% Source
13 cfg.srcpos=[size(x,2)/2,size(y,2)/2,1];
14 cfg.srcdir=[0 0 1];
15 cfg.srctype='disk';
16 cfg.srcparam1=[round(0.5/f) 0 0 0];
17
18 %% simulation parameters
19 cfg.seed=[hex2dec('623F9A9E')];
20 cfg.respin=5;
21 cfg.nphoton=10^8;
22 cfg.isreflect=1;
23 cfg.isrefint=1;
24 cfg.isnormalized=1;
25 cfg.isspecular=1;
26 cfg.issrcfrom0=0;
27 cfg.outputtype='flux';
28
29 %% time parameters
```

```
30 cfg.tstart=0;
31 cfg.tend=5e-9;
  cfg.tstep=5e-9;
32
33
  %% GPU settings
34
  cfg.autopilot=1;
35
  cfg.gpuid=1;
36
37
  %% Refraction index of couple agent
38
  n=[1 1.3 1.4 1.5 1.6];
39
40
  %% roughness
41
42 m_rand=rand(size(x,2),size(y,2));
  m_rand(m_rand <= 0.5) = 0;
43
  m rand (m rand>0.5) = 1;
44
45
   for cond = { 'liso', 'rug_ac', 'rug_agua', 'rug_ar'}
46
       k=1;
47
       disp(cellstr(cond))
48
       %% thickness CA variation
49
       for s_ac = 1:1:4 %mm
50
            %% refractive index variation
51
           for i=1:size(n,2)
52
                prop_ac=[10e-6 0 1 n(i)];
53
                %% selection of the roughness condition
54
                if strcmp(cond, 'liso')
55
                    prop_rug=[0.362517 11.1115 0.8 1.34];
56
                     ↔ %rug->epidermis
                elseif strcmp(cond, 'rug_ac')
57
                    prop_rug=prop_ac; %rug->CA
58
                elseif strcmp(cond, 'rug_agua')
59
                    prop_rug=[10^-6 0 1 1.3]; %rug->H20
60
                else
61
                    prop_rug=[10^-6 0 1 1]; %rug-> air
62
63
                end
                [vol,iac]=create_vol_rug(x, y, z, f,
64
                 \rightarrow s_ac,m_rand);
                cfg.vol=vol;
65
```

```
name=['var-c' num2str(s ac) '-n'
66
                 \rightarrow num2str(n(i) \star10) '-' char(cond)];
                cfq.session=name;
67
                 %% optical properties definition
68
                 cfg.prop=[0 0 1 1;
69
                10e-6 0 1 1;
70
71
                prop_ac;
                prop_rug;
72
                0.362517 11.1115 0.8 1.34
73
                0.09492 8.8799 0.9 1.4
74
                0.50797 8.8799 0.95 1.39
75
                 0.08286 8.8799 0.8 1.4
76
                 0.17957 8.8799 0.95 1.38
77
                0.09897 3.55196 0.75 1.44];
78
                %% simulation execution
79
                clc
80
                disp(name)
81
                tic
82
                 flux=mcxlab(cfg, 'cuda');
83
                tim=toc;
84
                 %% log file
85
                disp(['tempo execução: ' num2str(tim)]);
86
                 fileID=fopen('log_sim_fontes.dat', 'a');
87
                fprintf(fileID, 'Simulação: %s\t Tempo
88
                 fclose(fileID);
89
                 %% saving results
90
                resultado(k).data = flux.data;
91
                resultado(k).n = n(i);
92
                resultado(k).sac = s_ac;
93
                resultado(k).s_font = s_font;
94
                resultado(k).cfg = cfg;
95
                resultado(k).cond = cond;
96
                resultado(k).entropia = entropy(m_rand);
97
98
                k=k+1;
            end
99
        end
100
        save(['resultado_flux_disco_norm-' cond{1}
101
        \leftrightarrow '.mat'], '-v7.3');
```

102 **end**

B.3 Simulation script for oblique incidence

```
1 clear, clc, close all;
2 %% axis
3 x_mm=32;
4 y_mm=32;
5 z_mm=15.04;
6
7 fesc=0.08; %80 microns
8 x=1:(x_mm/fesc);
9 y=1:(y_mm/fesc);
10 z=1:(z_mm/fesc);
11
  %% Source
12
13 cfg.srctype='disk';
  cfg.srcparam1=[round(0.5/fesc) 0 0 0];
14
15
  %% setup simulation
16
  cfg.unitinmm=fesc;
17
  cfg.seed=[hex2dec('623F9A9E')];
18
19
  cfg.respin=5;
20
  cfg.nphoton=10^8;
21
22
  cfg.isreflect=1;
23
24 cfg.isrefint=1;
25 cfg.isnormalized=1;
26 cfg.isspecular=1;
  cfg.issrcfrom0=0;
27
28
  %% output type
29
  cfg.outputtype='flux';
30
31
  %% time parameters
32
  cfg.tstart=0;
33
34 cfq.tend=5e-9;
  cfg.tstep=5e-9;
35
36
```

```
37 %% GPU thread configuration
38 cfg.autopilot=1;
   cfg.gpuid=1;
39
40
  %% n ca
41
 n=[1 1.3 1.4 1.5 1.6];
42
43
44
  %% rughness
45
46 m_rand=rand(size(x,2),size(y,2));
47 s=0.5;
48 m rand (m rand \leq s) =0;
49 m_rand(m_rand>s)=1;
50
   % theta i variation
51
   for theta=0:10:30;
52
       k=1;
53
       cfg.srcdir=[sind(theta) 0 cosd(theta)];
54
       %% h_ca variation
55
       for s_coup = 1:1:4 %mm
56
           %% n_ca variation
57
           for i=1:size(n,2)
58
                % dx and dy caculation
59
                dx2=(s_coup/fesc) * sind(theta) / sqrt(n(i)^2
60
                \rightarrow -sind(theta)^2);
                dx1=((5.2-s_coup)/fesc) * tand(theta);
61
                dx=dx1+dx2;
62
                %% setup source position
63
                cfg.srcpos= [round((size(x, 2)/2)-dx),
64
                \leftrightarrow size(y,2)/2, 1];
65
                prop_coup=[10e-6 0 1 n(i)];
66
                prop_rug=[0.362517 11.1115 0.8
67
                %% volume genaration
68
                [vol, i_coup]=create_vol(x_mm, y_mm, z_mm,
69

→ fesc, s_coup, m_rand);

                cfg.vol=vol;
70
```
```
name=['var_n_camada_' num2str(s_coup) '_n'
71
                      num2str(n(i) *10) '_theta_'
                  \hookrightarrow
                  \leftrightarrow num2str(theta)];
                 cfg.session=name;
72
                 %% optical proprieties setup
73
                 cfg.prop=[0 0 1 1;
74
                 10e-6 0 1 1;
75
                 prop_coup;
76
77
                 prop_rug;
                 0.362517 11.1115 0.8 1.34
78
                 0.09492 8.8799 0.9 1.4
79
                 0.50797 8.8799 0.95 1.39
80
                 0.08286 8.8799 0.8 1.4
81
                 0.17957 8.8799 0.95 1.38
82
                 0.09897 3.55196 0.75 1.44];
83
84
                 %% run simulation
85
                 clc
86
                 disp(name)
87
                 tic
88
                 fluence=mcxlab(cfg, 'cuda');
89
                 tim=toc;
90
                 %% log file
91
                 disp(['Time execution: ' num2str(tim)]);
92
                 fileID=fopen('log_sim_fontes_ang.dat', 'a');
93
                 fprintf(fileID, 'Simulation: %s\t Time
94

    execution: %f\n', name, tim);

                 fclose(fileID);
95
                  %% write results
96
                 resultado(k).data = fluence.data;
97
                 resultado(k).n = n(i);
98
                 resultado(k).scoup = s_coup;
99
                 resultado(k).s_font = s_font;
100
                 resultado(k).cfg = cfg;
101
                 resultado(k).cond = cond;
102
                 resultado(k).theta = theta;
103
104
                 k=k+1;
105
            end
106
```

B.4 Simulation script for multiple sources

```
1 clear, clc, close all;
2 %% axis
3 x_mm=32.08;
4 y_mm=32.08;
5 z_mm=15.04;
6
7 fesc=0.08; %80 microns
8 x=1:round(x_mm/fesc);
9 y=1:round(y_mm/fesc);
10 z=1:round(z_mm/fesc);
11
12 %% source
13 cfg.srcdir=[0 0 1];
14 cfg.srctype='disk';
  cfg.srcparam1 = [round(0.5/fesc) 0 0 0];
15
16
17 %% setup simulation
  cfg.unitinmm=fesc;
18
  cfq.seed=[hex2dec('623F9A9E')];
19
20
21 cfg.respin=5;
22 cfg.nphoton=1e8;
23
24 cfg.isreflect=1;
25 cfg.isrefint=1;
26 cfg.isnormalized=1;
27 cfg.isspecular=1;
  cfg.issrcfrom0=0;
28
29
30 %% output type
   cfg.outputtype='flux';
31
32
```

```
%% time parameters
33
  cfg.tstart=0;
34
  cfg.tend=5e-9;
35
  cfg.tstep=5e-9;
36
37
  %% GPU thread configuration
38
39
  cfg.autopilot=1;
  cfg.gpuid=1;
40
41
  %% indice acoplador
42
  n=[1 1.3 1.4 1.5 1.6];
43
44
45
  %% Multiples sources parameters
46
  x_c = round((1+size(x, 2))/2);
47
   y_c = round((1+size(x, 2))/2);
48
49
   dx = round([0.5:1:3.5]/fesc);
50
   dy = round([0.5:1:3.5]/fesc);
51
52
  n_f = 4;
53
54
  %% roughness
55
  m_rand=rand(size(x,2),size(y,2));
56
  m_rand(m_rand <= 0.5) = 0;
57
  m_rand(m_rand>0.5) = 1;
58
59
  %% loop for each source
60
  k=1;
61
   for f=1:size(dx,2)
62
       p_x = [x_c-dx(f) x_c+dx(f) x_c-dx(f) x_c+dx(f)];
63
       p_y = [y_c+dy(f) y_c+dy(f) y_c-dy(f) y_c-dy(f)];
64
       %% source position
65
       for p_f=1:n_f
66
67
           cfg.srcpos=[p_x(p_f),p_y(p_f),1];
           %% h_ca variation
68
           for s\_coup = 1
69
                %% n ca variation
70
                for i=1:size(n,2)
71
```

72	prop_coup=[10e-6 0 1 n(i)];
73	prop_rug=[0.362517 11.1115 0.8 1.34];
	↔ %rug->epidermis
74	%% volume generation
75	<pre>[vol, i_coup]=create_vol(x_mm, y_mm, z_mm,</pre>
	\leftrightarrow fesc, s_coup, m_rand);
76	cfg.vol=vol;
77	%% setup name session
78	<pre>name=['camada_' num2str(s_coup) '_n'</pre>
	\rightarrow num2str(n(i) *10) '_d_' num2str(f)
	\leftrightarrow '_font_' num2str(p_f)];
79	cfg.session=name;
80	%% optical proprieties setup
81	cfg.prop=[0 0 1 1;
82	10e-6 0 1 1;
83	prop_coup;
84	prop_rug;
85	0.362517 11.1115 0.8 1.34
86	0.09492 8.8799 0.9 1.4
87	0.50797 8.8799 0.95 1.39
88	0.08286 8.8799 0.8 1.4
89	0.17957 8.8799 0.95 1.38
90	0.09897 3.55196 0.75 1.44];
91	%% run simulation
92	disp(name)
93	tic
94	<pre>fluence=mcxlab(cfg, 'cuda');</pre>
95	<pre>tim=toc;</pre>
96	%% arquivo log
97	<pre>disp(['time execution: ' num2str(tim)]);</pre>
98	fileID=fopen('log_sim_multi_fontes_n.dat'
	<pre> , 'a'); </pre>
99	<pre>fprintf(fileID, 'Simulation: %s\t Time</pre>
	\leftrightarrow execution: %f\n', name, tim);
100	<pre>fclose(fileID);</pre>
101	%% Write results
102	resultado(k).data = fluence.data;
103	resultado(k).n = n(i);
104	resultado(k).scoup = s_coup;

resultado(k).font = p_f ; 105 resultado(k). $p_x = p_x(p_f);$ 106 resultado(k).p_y = $p_y(p_f)$; 107 resultado(k).cfg = cfg;108 k=k+1;109 end 110 end 111 end 112 k=1; 113 save(['resultado_dx_' num2str(dx(f)) '_dy_' 114 \rightarrow num2str(dx(f)) '_norm_multifontes_401.mat'], \leftrightarrow '-v7.3');

115 **end**

APPENDIX C – CHAPTER 5 SCRIPTS

C.1 Script for reflective material optical properties validation

```
1 clear, close all, clc;
2
3 cfg.nphoton=1e8;
4 x = [1:240] . *0.25;
5 z = [1:20] . *0.25;
6 % Volume defintion
7 cfg.vol=uint8(ones(240,240,20));
8 i_i=10;
9 i_f=15;
10 cfg.vol(:,:,i_i:i_f)=2;
11 % Source parameters
12 cfg.srcpos=[120 120 1];
13 cfg.srcdir=[0 0 1];
14 cfg.srctype='cone';
15 cfg.srcparam1=[0.9 0 0 0];
16 %simulation parameters
17 cfg.unitinmm=0.25;
18 cfg.respin=5;
19 cfg.isreflect=1;
20 cfg.isrefint=1;
21 cfg.isnormalized=1;
22 cfg.isspecular=1;
23 %time parameters
24 cfg.tstart=0;
25 cfg.tend=5e-9;
  cfg.tstep=5e-9;
26
27
28 % test varing n
  figure('units', 'normalized', 'outerposition', [0 0 1 1]);
29
  for i=2:7
30
       cfg.prop=[0 0 1 1;10e-6 0 1 1;10e-6 1 -1 10^i];
31
       % run simulation
32
33
       flux=mcxlab(cfg);
      res_n(i).data=flux;
34
```

```
res_n(i).prop=cfg.prop(3,:);
35
       %_____
36
       % plot results
37
       subplot(2,3,i-1)
38
       imagesc(x, z,
39
       → log10(squeeze(flux.data(120,:,:)*cfg.tend))');
      hold all
40
       caxis([-8 1])
41
      plot([0 60],[i_i-0.5 i_i-0.5]*cfg.unitinmm,'-w')
42
43
      plot([0 60],[i_f+0.5 i_f+0.5]*cfg.unitinmm,'-w');
      xlim([15 45])
44
      title(['n = 10^{\prime} num2str(i) ])
45
      xlabel('x (mm)')
46
      ylabel('z (mm)')
47
48 end
49 c=colorbar;
50 c.Location='east';
51 c.Position=[0.9200 0.1000 0.0150 0.8200];
52 colormap jet;
53 ylabel(c, 'Log_{10} (flux)')
54 set(findall(gcf, '-property', 'FontWeight'), 'FontWeight',
   ss set(findall(gcf, '-property', 'FontSize'), 'FontSize', 18)
56 saveas(gcf, 'val.fig')
save(['validacao.mat'],'-v7.3');
```

C.2 Volume inicialization

```
1 function [vol,i_tec,i_f]=create_vol_metal(x_mm, y_mm,
   \hookrightarrow z_mm, fesc)
2
       x=x_mm mm e y= y_mm mm z=12.42 mm
3
       x=1:(x_mm/fesc);
4
       y=1:(y_mm/fesc);
5
       z=1:(z_mm/fesc);
6
7
      %% Thickness
8
       i_tec=round(2.5/fesc);
9
10
       s(1) = round(0.08/f); %Epidermis
11
```

```
s(2) = round(0.160/f); %Papillary dermis
12
13
       s(3) = round(0.08/f); %Dermis with superficial vascular
        → network
       s(4) = round(1.52/f);%Reticular dermis
14
       s(5) = round(0.08/f); %Dermis with deep vascular
15
        → network
       s(6) = round(8/f); %Hypodermis
16
       %% positions
17
       p=0;
18
19
       for i=1:size(s,2)
            if i==1
20
                p(i) = i_{tec+s}(1);
21
            else
22
                p(i) = p(i-1) + s(i);
23
            end
24
       end
25
       %% volume
26
       vol=uint8(ones(size(x,2),size(y,2),size(z,2)));
27
       for i=1:size(s,2)
28
            if i==1
29
                vol(:,:,i_tec:p(i))=1+i;
30
            else
31
                vol(:,:,p(i-1):p(i))=1+i;
32
            end
33
            i f = 1 + i;
34
       end
35
   end
36
```

C.3 Simulation script

```
1 clear, clc, close all;
2 addpath(pwd)
3
4 cfg.nphoton=10^8;
5 fesc = 0.08;
6
7 x_mm=32;
8 zaux=12.42;
9
```

```
10 [vol,z_tec,i_f] = create_vol_metal(x_mm, x_mm, zaux,
   \hookrightarrow
       fesc);
11
12 x=1: (x_mm) / fesc;
   z=1:(zaux/fesc);
13
14
  f_derm=4.42;
15
16
   cfq.vol=vol;
17
18
  %% source setup
19
20 cfg.srcpos=[16/fesc 16/fesc 1];
21 cfg.srcdir=[0, 0, 1];
22 cfg.srctype = 'disk';
23 \text{ cfg.srcparam1} = [1 \ 0 \ 0 \ 0];
24 %% simulations parameters
25 cfg.unitinmm=fesc;
  cfg.respin=5;
26
27
28 cfg.isreflect=1;
29 cfg.isrefint=1;
  cfg.maxdetphoton = 10^8;
30
31
32 r_det = 1;
   r_fonte = 1;
33
34
   %% optical proprieties setup
35
   cfg.prop=[0 0 1 1;
36
           10e-6 0 1 1
37
            0.362517 11.1115 0.8 1.34
38
            0.09492 8.8799 0.9 1.4
39
            0.50797 8.8799 0.95 1.39
40
            0.08286 8.8799 0.8 1.4
41
            0.17957 8.8799 0.95 1.38
42
            0.09897 3.55196 0.75 1.44
43
            10e-6 1 -1 1e6];
44
45
  %% time parameters
46
47 cfg.tstart=0;
```

```
cfq.tend=5e-9;
48
   cfg.tstep=5e-9;
49
50
  %% GPU thread configuration
51
  cfg.autopilot=1;
52
  cfg.gpuid=1;
53
54
  %% detctor position
55
  cfg.detpos=[cfg.srcpos(1)+4, cfg.srcpos(1), z_tec-1,
56
   \rightarrow r_det;
       cfg.srcpos(1), cfg.srcpos(1), f_derm/fesc, r_det]; %
57
        ↔ comment if run without detctor
   %cfg.detpos=[] % uncomment if run without detector
58
59
  aux i=0;
60
61
  i=6:3:40;
62
  i=[1 i];
63
   for i=i
64
       clc
65
       aux_i=aux_i+1;
66
       disp(i);
67
       if i==1
68
            %% source path
69
            shape{1}=struct('Cylinder', struct('Tag',0,'C0',
70
             \leftrightarrow [cfg.srcpos(1)+4 cfg.srcpos(1) 1], 'C1',
                [cfg.srcpos(1)+4 cfg.srcpos(1) z_tec-1], 'R',
             \hookrightarrow
             \leftrightarrow r fonte));
            if cfg.detpos ~= []
71
                 %% Detctor 2 path
72
                 shape{2}=struct('Cylinder', struct('Tag', 0,
73
                 → 'CO', [cfg.srcpos(1) cfg.srcpos(1)
                     f_derm/fesc], 'C1', [cfg.srcpos(1)
                 \hookrightarrow
                     cfg.srcpos(1) zaux/fesc], 'R', r_fonte));
                  \hookrightarrow
74
            end
            %% define shapes
75
            cfg.shapes = savejson('Shapes', shape);
76
            %% result variable
77
            resultado(aux_i).label='Without reflector';
78
```

```
resultado(aux i).r = 0;
79
        else
80
             % Reflective material
81
             shape{1}=struct('Cylinder', struct('Tag', i_f+1,
82
                 'CO', [cfg.srcpos(1) cfg.srcpos(1) 1], 'C1',
              \hookrightarrow
                 [cfg.srcpos(1) cfg.srcpos(1) z_tec-1], 'R',
              \hookrightarrow
                 i));
              \hookrightarrow
             % Source path
83
             shape{2}=struct('Cylinder', struct('Tag', 1, 'C0',
84
              \hookrightarrow
                 [cfg.srcpos(1) cfg.srcpos(1) 1], 'C1',
                 [cfg.srcpos(1) cfg.srcpos(1) z_tec-1], 'R',
              \hookrightarrow
              \leftrightarrow r fonte));
             if cfg.detpos ~= []
85
                  % Detector 1 path
86
                  shape{3}=struct('Cylinder', struct('Tag', 0,
87
                   \rightarrow 'CO', [cfg.srcpos(1)+4 cfg.srcpos(1) 1],
                   \rightarrow 'C1', [cfg.srcpos(1)+4 cfg.srcpos(1)
                   \leftrightarrow z_tec-1], 'R', r_fonte));
                  % Detector 2 path
88
                  shape{4}=struct('Cylinder', struct('Tag', 0,
89
                   → 'CO', [cfg.srcpos(1) cfg.srcpos(1)
                     f_derm/fesc], 'C1', [cfg.srcpos(1)
                   \hookrightarrow
                      cfg.srcpos(1) size(z,2)], 'R', r_fonte));
                   \hookrightarrow
             end
90
             % shape defition
91
             cfg.shapes = savejson('Shapes', shape);
92
             resultado(aux_i).r = i*cfg.unitinmm;
93
             resultado(aux i).label=['Reflector radius: '
94
                  num2str(i*fesc) ' mm'];
              \hookrightarrow
        end
95
         %% run simulation
96
         [flux,detp,vol]=mcxlab(cfg);
97
         %%write results
98
        resultado(aux_i).data=flux.data;
99
        resultado(aux_i).stats=flux.stat;
100
        resultado(aux_i).cfg=cfg;
101
        resultado(aux i).detp=detp;
102
        resultado(aux_i).vol = vol;
103
        cfq.vol=vol.data;
104
```