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Full Length Research

3-dimensional simulation of light transport in tissue using a steady state monte carlo method for photodynamic therapy application

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ABSTRACT: Photodynamic therapy (PDT) is a developing treatment modality for cancer and surface carcinomas that uses a combination of non-ionizing light in the presence of a photosensitizing (PS) agent and oxygen to produce singlet oxygen that can be combined with other physiological factors to cause an organ cells death of the target area. This research simulates the propagation of light photons through normal tissue and tissue incubated with a PS agent (Metvix – Methyl Aminolevulinate (MAL)) and prepped for PDT procedure. Using the Hop/Drop/Spin nomenclature, the photons, after being allocated a weight, are allowed to take random step-size through the tissue as they are attenuated by the tissue and the presence of the photosensitizing agent while accounting for the degradation of the PS agent as the process proceeds. In each step, a fraction of the photon's weight is deposited into allocated three-dimensional Cartesian bin. In comparison with normal tissue, the result from tissues prepped with the PS agent showed increased divergence of photon's spatial trajectory, increment in photon penetration depths and overall attenuation. The introduction of the PS agents into tissue during PDT causes improvement in the overall attenuation of the tissue, and this improvement in attenuation can be used for accurate localization of treatment area during PDT procedures and, combined with other photodynamic factors, used for calculating the effective photon dose (PD).

Keywords: 3-dimensional simulation, light transport, photodynamic therapy, photosensitizing agents.

INTRODUCTION

Photodynamic therapy (PDT) is a developing treatment modality based on the interaction of non-ionizing light, a photosensitizing drug, and oxygen (Zhu and Finlay, 2008; Ashley and Martin, 1995). The PDT process is a very sensitive process and can be easily prone to physiological vagaries on application. It requires an accurate combination of a light source (usually Lasers or Light Emitting Diodes) and its induced energy, a photosensitizing agent (which usually metabolizes to the photoactive element Protoporphyrin – PpIX) which has a characteristic predilection for the induced photon energy, and oxygenation of the target area. This combination tends to increase the temperature of such targeted area, induces florescence photo-bleaching of the photo-sensitizers, and/or produce singlet oxygen. This process can ablate tissue, induce plasma formation and create mechanical damage in tissue that most times results in the death of targeted cells in the tissue (Salas-García et al., 2012a; Fanjul-Vélez et al., 2009).

Uncertainty or imprecision in any of the three components of consideration, or a slight shift in optimization can lead to uncontrollable effects (which, due to the manifold and complex possibilities and the outcome of interaction of these components, are usually stochastic in nature) or no effect at all (Zhu and Liu, 2012; Flock et al., 1989). Therefore, each component has to be quantified spot-on to achieve expected and desirable physiological effect (usually apoptosis of the cells in the target tissue) during photodynamic therapy and a proper simulation of light transport through tissue would form a foundation upon

which dosimetry and optical, anatomical imaging can be developed and improved on (Zhu and Finlay, 2008; Flock et al., 1989).

Therefore, the objective of this study is to simulates the propagation of light photons through normal tissue and tissue incubated with a PS agent (Metvix – Methyl Aminolevulinate (MAL)) and prepped for PDT procedure.

MATERIALS AND METHODS

The simulation for this research study was executed using MATLAB R2018a script file. It involves inserting or launching one photon at a time into the tissue, and while using the Hop-Drop-Spin nomenclature designed by Steven L. Jacques (Jacques and Wang, 1995; Wilson and Adam, 1983), track the trajectory of each photon as it is being scattered and absorbed through the tissue. The photons are projected at x, y, z initial positions and their trajectory tracked by conditional directional cosines.

The photon is allowed to travel a random distance before it interacts with the tissue. This distance is based on a random number and the localized attenuation coefficient of the tissue (normal tissue, or tissue prepped with PS agent for PDT). For normal tissue, the total attenuation coefficient μ_t is;

$$\mu_t = \mu_a + \mu_s \quad (1)$$

where μ_a is the absorption coefficient and μ_s the scattering coefficient. But, in order to calculate the progressive degrading effects of the PS agent on the attenuation of tissues prepped for PDT, seven stiff differential equations proposed by Salas-Garcia et al. (2012b) was invoked. Then, using Fick's law to characterize the inhomogeneous photosensitizer precursor distribution, and to calculate the concentration reached at each point of the tissue during incubation, the temporal concentration was calculated as;

$$M(t) = M_0 \int_0^t \left(\frac{K}{\sqrt{D\pi t'}} e^{-\frac{z^2}{4Dt'}} - \frac{K^2}{D} e^{\frac{K}{D}z} e^{\frac{K^2}{D}t'} erfc\left(\frac{K}{\sqrt{D}}\sqrt{t'} + \frac{z}{2\sqrt{Dt'}}\right)\right) e^{-\frac{t'}{\tau}} dt' \quad (2)$$

Where: $D =$ the diffusion coefficient through the epidermis and dermis, $M =$the pro-drug concentration, $z =$the depth in the tissue, $K =$ the permeability of the diffusion barrier, $t =$ the relaxation time of the precursor as a consequence of the process of generation of PS, $\tau =$ the conversion rate of PS precursor in it's photoactive compound, $M_0 =$ is the concentration of PS precursor in the skin surface at time $t = 0$.

When this concentration is known at each point, the accumulated concentration of active substance S_0 during the incubation period is calculated as;

$$S_0(t) = \varepsilon_p \frac{\tau_p}{\tau_{a\to p}} M(t) \quad (3)$$

The concentration is used to calculate the PS agent absorption coefficient μ_{a_PS} such that;

$$\mu_{a\_PS} = \sigma_{psa}.[S_0] \quad (4)$$

where σ_{psa} is the absorption cross-section of PpIX molecules at the treatment wavelength.

To update equation (1), the total attenuation coefficient of the tissue incubated with photosensitizers becomes;

$$\mu_t = \mu_a + \mu_s + \mu_{a\_PS} \quad (5)$$

Note the value of μ_{a_PS} keeps changing as the treatment proceeds, and the solutions were obtained by solving a set of seven stiff differential equations (Salas-Garcia et al., 2012a). Note also that the total attenuation coefficient described by equation (5) represents the dynamic behavior of the PS absorption coefficient during PDT.

After the total attenuation coefficient has been calculated, the photon is assigned a photon weight, and as it interacts with the tissue this assigned weight is reduced by reflection at the entrance surface, absorption and transmittance at the outer surface. The remaining photon weight that is not reflected at the surface, transmitted through the tissue or absorbed within the tissue continues propagation. As they propagate through the tissue, they are redirected according to a scattering or phase function that describes the angular dependence of single scattering by the particular tissue until its value falls below an assigned threshold of photon's weight.

The fraction of light that is directly reflected from such surfaces depends on the angle of incidence of the incident photon and the refractive indices of both media. Neglecting the effects of polarization, the angular dependence of internal reflection R_i, is calculated using Fresnel's equation;

$$R_i = \frac{(\sin\theta_1\cos\theta_2 - \cos\theta_1\sin\theta_2)^2}{2} \times \frac{((\cos\theta_1\cos\theta_2 + \sin\theta_1\sin\theta_2)^2 + (\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2)^2)}{((\sin\theta_1\cos\theta_2 + \cos\theta_1\sin\theta_2)^2((\cos\theta_1\cos\theta_2 + \sin\theta_1\sin\theta_2)^2)} \quad (6)$$

Where: $\cos\theta_1$, $\sin\theta_1$, $\sin\theta_2$, $\cos\theta_2$, n_1 and n_2 were the incident trajectory (uz), incident trajectory $(1 - uz^2)^{1/2}$, transmitted trajectory $(\sin\theta_1(^{n_1}/_{n_2}))$, transmitted trajectory $((1 - \sin\theta_1^2)^{1/2})$, refractive index of incident medium (n_{tissue}) and the refractive index of transmitted medium (n_f)

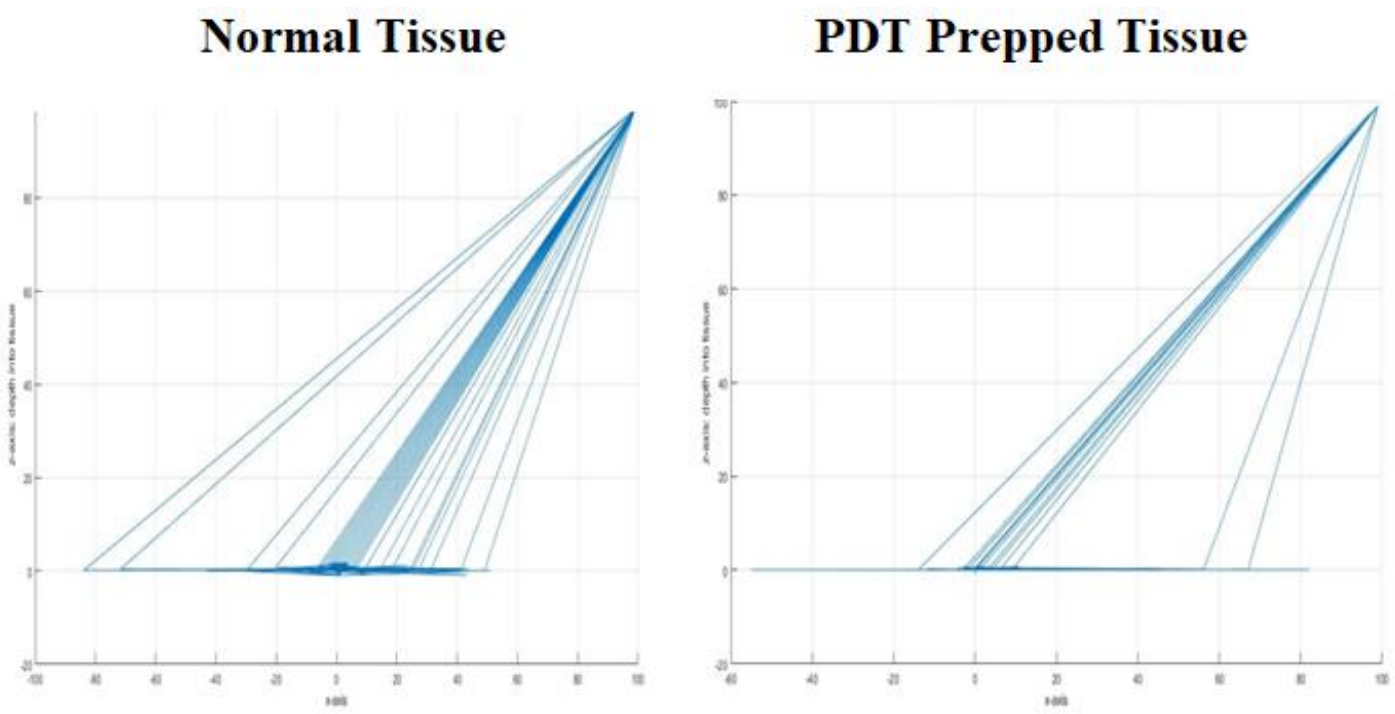

Figure 1. shows the trajectory of the photons that were reflected at the surface of the tissue.

Note: For unit irradiance, the fraction of light transmitted is;

$$T = 1 - R_i \quad (7)$$

The scattering of the photons during propagation according to Mie's theory are randomly distributed in all directions using a spherical coordinate system. The details of the photon path, absorption, scattering, reflection and transmission are recorded and plotted, and this gives a description of the transport of light through normal tissue, and tissue prepped with PS for PDT. This research study focuses on the steady-state design of the Monte Carlo simulation of light transport (Farrell et al., 1992; Agostinis et al., 2011).

RESULTS

After the simulation was run for 1,000 photons, patterns began to emerge as the random step size taken by each photon was traced in a Cartesian 3-D plot. These photons were launched at normal tissue, and then later on at tissues prepped for PDT incubated with a PS agent. The plots obtained for both cases were that of the trajectories of the reflected photons at the boundary surface of the tissue as shown in Figure 1 and absorption occurring within the tissue as the photons propagates and deposits its weight into pre-allocated bins (Donnelly et al., 2007; Keller et al., 2010) as shown in Figure 2.

Note that for normal tissue, the hip of accumulated photons is much more significant than for that of PDT prepped tissue. This difference is due to the fact that more photons penetrate into PDT prepped tissue than normal tissue (Li et al., 2004; Liu et al., 2010). Thus, the presence of PS agent in tissue reduces the surface reflectance of the tissue.

DISCUSSION

The result and analysis of the simulation shows that the PS effect on the absorption and scattering coefficient of normal tissue improved significantly and it is easily noticeable. The presence of PS agent also improves the lateral absorption and distribution of photons (Liu et al., 2003; Lux and Koblinger, 1991; Metropolis and Ulam, 1949). This improvement in attenuation is important in localization of treatment area during PDT. A properly localized treatment area would reduce damage to healthy tissue surrounding the targeted carcinoma and improve the estimation of the photon dose to such target area. Although Liu et al. (2010) proposed a one-dimensional model to simulate the dynamic process of ALA-PDT of normal human skin, the model from this research study can be used as the foundational platform with which to convert the one-dimensional modeling of the ALA – PDT into a 3 – dimensional model: this would make the result they obtain easier to interpret (Liu et al., 2010; Reble et al., 2010). The findings from this research study are also a corroborative of the study carried out by other researchers

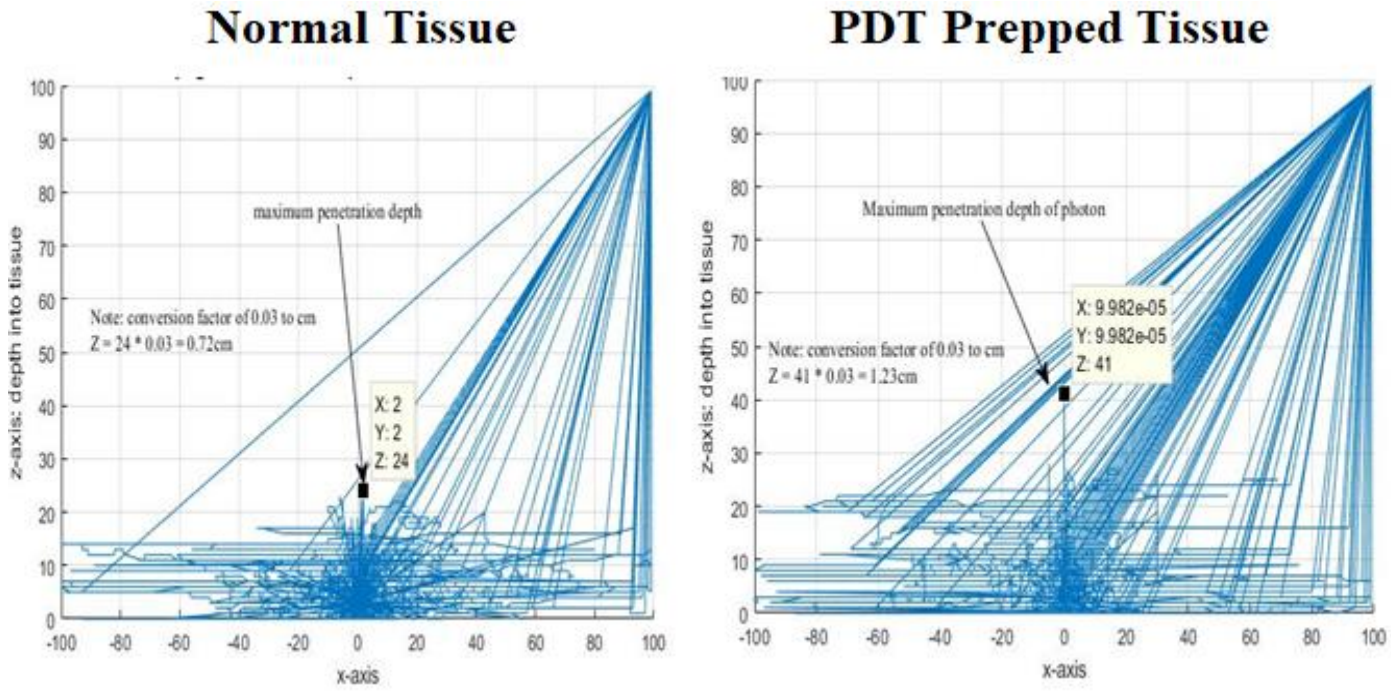

Figure 2. Shows an x-z view of the trajectory of photons what were absorbed by normal tissue and tissue prepped for PDT procedure.

reviewed such as Salas-García et al. (2012b), Caigang and Quan (2012), and Steven (2014).

Conclusion

The result of the simulation shows that improved attenuation and penetration of light can be achieved in the presence of a PS agent when light photons propagates through target tissues during photodynamic therapy. The application of photodynamic therapy in the treatment of cancers and surface carcinomas is still limited due to the difficulties involved in managing the manifold changes that occur during the PDT process. The findings from this research can be used as a foundation on which most of the physics related changes (photo-physics) is based. Thus, paving way for the improvement on the nature and control of PS properties towards quantifying the accrued effects of the produced singlet oxygen and heat generated during the PDT procedure. It is thus obvious that the results from the research is not absolute nor independent, but liable to improvements and depend also on improvements in other fields of study with the hope to tackle the manifold problems that limits our use of PDT for a lot more detailed and practical medical procedures.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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