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Research Article

Simulation of Time and Frequency Domain of Photosensitizers Effect During Light Transport through Tissue as Applied to Photodynamic Therapy using a Steady State Monte Carlo Method with Simulink

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Abstract

Photodynamic therapy (PDT) is a treatment process that makes use of a non-ionizing light source targeted at specific section of cells (a tumor) in order to induce apoptosis, and eventually, the death of cells in such area. This is achieved using specific light sensitive photosensitizing (PS) agents (in the case of this research Metvix-Methyl Aminolevulinate (MAL)) used to saturate the treatment area for a recorded time period before irradiating with non-ionizing light source. This research was designed to observe the time and frequency domains as the PS signal decays during the PDT process. During the process, the PS agent degenerates and becomes less and less interactive with the light source. Using the Hop/drop/spin nomenclature, the source of the incident photon is simulated using A Gaussian White Noise (AGWN) on Simulink and the incident signal is allowed to attenuate through the target area while the time and frequency domain of the photosensitizer MAL is recorded as it decays. It is observed that the amplitude of the absorption coefficient of the PS agent dropped to almost 0 during a short sample time while the normalized frequency decays with a highly damped and irregular oscillatory pattern. The improvement in attenuation due to the presence of the PS agent degenerates sharply during the initial state of the treatment in order to ensure that the generation of singlet oxygen terminates just after treatment time.

Introduction

Photodynamic therapy is a photochemical process involving the combination and interaction of non-ionizing light, a photosensitizing agent (PS) and Oxygen (Zhu et al, 2008) all interacting in the presence of an abnormal mass of tissue to ablate it. The process has been approved to treat various types of cancer and tumor-like clusters, and unlike radiation therapy, it can be administered repeatedly without cumulative long-term complication since it doesn't appear to have any effect on the DNA of targeted cells [1]. The presence of PS agent combined with the incident light activates singlet Oxygen, $^1O_2$ in the presence of Oxygen within the cell. It is the singlet Oxygen combined with the amount of heat generated during irradiation that induces cell death [2]. Thus the PDT process continues in the presence of any source of light (sunlight for example) as long as there are PS agents present within the treatment area. So in order to execute proper treatment planning with precise fractionation, it is important to be able to understand, control, work with and manage the rate of decay of the PS agent during treatment.

Various PS drugs have been generated to cater for varying light wavelength predilection, penetration depth, attenuation and duration during treatment (Zhu et al, 2008). For proper treatment planning and fractionation, the use of the right quality and quantity of the PS is essential to ensure minimum damage to surrounding tissue and maximum damage to target tissues [3]. Therefore, the objective of this study is to quantify the time and frequency decay of the photosensitizer MAL and to describe the time rate of decay of the PS in focus.

Materials and Methods

The process of PS decay during PDT was simulated on MATLAB-Simulink R2018a platform. The entire simulation was designed on the Hop/drop/spin nomenclature [4,5] with some special modification due to the work structure of the Simulink environment. Light photon injected into the target area is allowed to bounce around, drop some its initial assigned weight and spun in a semi-random direction which is determined by the direction of the incident light and the overall attenuation coefficient of the treatment area. The photon, having being given an initial photon weight loses some of this weight as it is reflected at the entrance surface, attenuated within the tissue or eventually transmitted through as it loses its photon weight. It is discarded as soon as the initial assigned photon weight drops below a stipulated threshold value, and another photon is injected to go through the same process over again.

When a large amount of protons goes through this process, the PS agent and its attenuation effect is diminished over time. To calculate and keep track of the degradation process seven stiff differential equations proposed by Salas-Garcia et al. [6] is simulated over a White Gaussian Noise (AWGN). To calculate the concentration of the PS agent within the treatment area attained during the incubation process, Fick's law used to characterize the inhomogeneous behavior of the PS agent is applied;

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

Where:
D is 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,
τ the conversion rate of PS precursor in its photoactive compound,
M_0 is the concentration of PS precursor in the skin surface at time t=0.
Figure 1 shows the Simulink formation used to calculate the concentration of the PS agent at each point in time during the simulation.

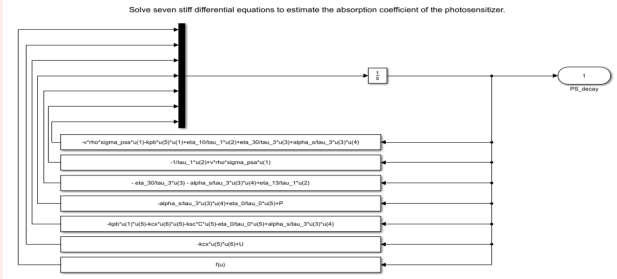

Figure 1: Shows the internal layout of the block for calculating the PS decay from solving seven stiff differential equations.

Result

From figure 2, the amplitude of the absorption coefficient of the PS begins at 5 × 10^7 and drops to almost 0 in a sample time of 50. This very fast drop ensures that the PS effect isn't long lasting and renders the effect of the PS negligible after treatment. Further emphasis on how the PS decays is seen from the frequency plot of the PS decay in figure 2. The magnitude of the PS agent drops from about 185dB to 160dB in less than 0.06 normalized frequency. After a little trough at 168dB in magnitude, the PS decays down to a terminal value below 150dB for the rest of the normalized frequency.

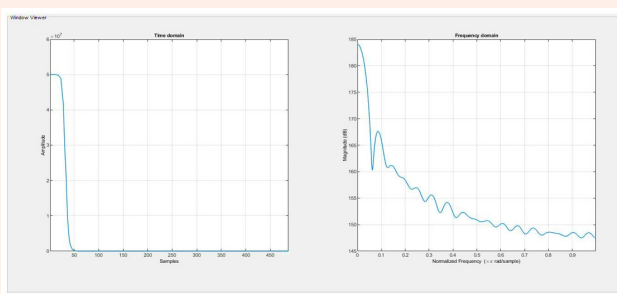

Figure 2: Shows the time and frequency domains of the decay of the PS during PDT process.

Discussion

This research study shows that the improved attenuation by the PS declines sharply and is short-lived as shown in figure 2. This is of importance as it determines dose fractionation and treatment frequency during treatment planning. In addition, it ensures that the process of improved photon attenuation does not continue after treatment when the patient is exposed to other sources of non-ionizing radiation like sunlight and electrical lights. Applying the result from the temporal decline of the attenuation coefficient of tissue prepped with PS for PDT, as depicted by the time and frequency domain of the PS decay of this research, the photo-kinetics (in near real-time) can be incorporated into the computational device Dosie TM (a new experimental integrated hardware and software device that calculates the light transport and photo-kinetics for PDT) (Beeson et al. (2019)). This could improve the calculation of light transport and cure index for the PDT process.

Conclusion

The application of PDT 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 [7,8] 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 chemist to improve on the nature and control of PS properties, and the biologist to understand and help quantify the accrued effects of the produced singlet oxygen and heat generated during the PDT procedure [9-11]. It is thus imperative to state here that the result from the research is not absolute, nor is it independent of other findings. The Simulink block formation and structure used for both the entire simulation and that of the PS concentration is liable to improvements and depends also on improvements in other fields of study which hope to tackle the manifold problems that limits our use of PDT for a lot more detailed and practical medical procedures.

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