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Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXI

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Influence of the photosensitizer photobleaching in the propagation of light during Photodynamic Therapy

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ABSTRACT

Photodynamic Therapy (PDT) is an optical treatment modality used to destroy malignant tissues. Nowadays there are fixed clinical PDT protocols that make use of a particular optical dose, photosensitizer amount and drug-light interval. However the treatment response varies depending on the type of pathology and the patient. In order to adjust current dosimetry to get an optimal treatment outcome, the development of accurate predictive models has emerged as the ideal tool to achieve new personal protocols. Several attempts have been made in this way although the influence of the photosensitizer distribution on the optical parameters has not been taken into account until this moment. We present a first approach to predict the spatial-temporal variation of the absorption coefficient during the photodynamic process applied to a dermatological disease taking into account the photobleaching of a topical photosensitizer. The model presented also takes into account an inhomogeneous initial distribution of the photosensitizer, the propagation of light in the biological media and the evolution of the molecular concentrations of different components involved in the photochemical reactions. The obtained results permit us to investigate how the depletion of the photosensitizer during the photochemical reactions affects to the light absorption as it propagates within the target tissue.

Keywords: Photodynamic Therapy, photosensitizer, absorption coefficient, skin disease.

1. INTRODUCTION

Photodynamic Therapy (PDT) is an optical treatment modality used in several clinical fields to destroy malignant tissues. It consists on the administration of a photosensitive substance which is activated by the posterior irradiation of the tumoral area[1]. As a consequence reactive oxygen species are produced and destroy the cancerous cells. Nowadays there are fixed clinical PDT protocols that make use of a particular optical dose, photosensitizer amount and drug-light interval. However the treatment response varies depending on the type of pathology and the patient[2, 3]. In order to adjust current dosimetry to get an optimal treatment outcome, the development of accurate predictive models has emerged as the ideal tool to achieve new personal protocols. Several attempts have been made in this way developing models that take into account the main photophysical processes involved in PDT such as the photosensitizer distribution, the light propagation within the tissue, the oxygen supply or the photochemical interactions[4, 5]. Regarding light propagation, most of these works use Monte Carlo (MC) implementations to obtain the light absorption in the target tissue taking into account the tissue optical properties. However, the influence of the photosensitizer distribution on the optical parameters has not been taken into account until now and could be of great interest to accurately estimate not only light propagation within the tissue but also the photosensitizer degradation in an in vivo real time PDT application. Both issues are essential to develop real time monitoring techniques that permit to properly interpret the measurements obtained, as well as to define an optimal dosimetry with a personal treatment planning purpose.

Apart from the characteristics of the radiation source, the propagation of light in a biological media is decisively affected by its optical properties[6]. These optical properties vary depending on the excitation light wavelength and the tissue composition and morphology. Therefore the light propagation modeling should take into account all of them to get an accurate result. If we want to obtain the optical radiation distribution during PDT, the process gets complex due to the incorporation of a photosensitive substance, or photosensitizer, to trigger a photochemical interaction between the excitation optical radiation and the target tissue. Moreover it is desirable to take into account the dynamic nature of the

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photochemical reactions involved, to get the spatial and temporal photosensitizer concentration and its influence in the excitation light absorption. This gives way to an initial baseline for later studies of the optical properties variations induced by the photosensitizer in biological media during PDT. In this work we present a first approach to predict the spatial-temporal variation of the photosensitizer absorption coefficient during the photodynamic process applied to a dermatological disease taking into account the photobleaching of a topical photosensitizer. The model presented in section 2 also takes into account an inhomogeneous initial distribution of the photosensitizer, the propagation of light in the biological media and the evolution of the molecular concentrations of different components involved in the photochemical reactions. The obtained results and their discussion are shown in section 3 and permit us to investigate how the depletion of the photosensitizer during the photochemical reactions affects to the light propagation in the target tissue. Final conclusions are presented in section 4.

2. ABSORPTION COEFFICIENT VARIATION DURING PDT

In order to get an accurate characterization of the photophysical phenomena that take place during PDT, it is required to take into account its dynamic nature. This implies the knowledge of the spatial and temporal evolution of the molecular components involved in the photodynamic reactions as well as those parameters that affect light propagation in the biological media. The concentration of the molecular components allow to study the production of reactive oxygen species like singlet oxygen that can be used as an indicator of the short term PDT effects. However it is not possible to trigger this kind of light tissue interactions without the appropriate irradiation. Thus the knowledge of the optical radiation distribution and hence of the media optical parameters becomes essential to get a correct estimation of the whole PDT treatment. Among these optical parameters, the absorption coefficient permits to quantify the absorption, which is the main mechanism responsible for triggering the photochemical reactions involved in PDT. So far, the modeling of light propagation in a biological media has been obtained taking into account only the target tissue optical parameters. These optical parameters are fixed for each kind of tissue and depend on the wavelength of the excitation optical source employed to excite the photosensitizer. However the administration of a photoactive substance in the tumor tissue modifies its absorption coefficient depending on the substance molecular concentration and as a consequence changes can be expected in the final optical distribution. Therefore the amount of photosensitizer accumulated in the tumor during the incubation period as long as its degradation as the irradiation is applied, will be also of great importance when calculating the optical radiation distribution. This is one of the reasons why the model presented below also considers the amount of photosensitizer that accumulates in the tumor tissue during the incubation period prior to the application of light.

2.1 Photosensitizer distribution and initial photosensitizer absorption coefficient

Methyl Aminolevulinate (MAL) is a prodrug that is endogenously metabolized to the photoactive element Protophorphyrin IX (PpIX). After its application on the skin surface, a diffusion process through the different skin layers occurs and it is converted to PpIX. Several studies have evaluated the PpIX content of the skin using fluorescence techniques and the influence of the stratum corneum as the main barrier to the diffusion of the photosensitizer to deeper layers of skin[7, 8].

The inhomogeneous distribution of a topical photosensitizer precursor through the skin and the photosensitizer endogenously produced play an important role to determine the concentration of photosensitizer to be accumulated during the incubation period. For this reason we used the Fick's law to characterize the inhomogeneous photosensitizer precursor distribution and to calculate the concentration reached at each point of the tissue during the incubation period. According to Fick's law, if there are differences of concentration of a substance, its molecules move from higher to lower concentration regions, so the flow of substance goes in the opposite direction of the concentration gradient.

$$J = -D\frac{\partial M}{\partial z} \tag{1}$$

Where J is the flux vector indicating the direction and magnitude of substance, D is the diffusion coefficient, M is the prodrug concentration and z is the depth in the tissue. The distribution of the photosensitizer in the skin is limited by several factors, including the stratum corneum which acts as a diffusion barrier and is characterized by the permeability, K , the diffusion coefficient through the epidermis and dermis, D , the relaxation time of the precursor as a consequence of the generation of the photosensitizer and other processes (lymphatic flow and blood perfusion), τ , and

the conversion rate of photosensitizer precursor in its photoactive compound[9]. The temporal evolution of the photosensitizer precursor concentration for each depth in the tissue sample can be calculated as

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

where M_o is the concentration of photosensitizer precursor in the skin surface at t=0 and z is the distance from the corneal layer located at z=0.

Once the concentration of the photoactive compound precursor is known at each point, the accumulated concentration of active substance S_0 in the tissue is calculated during the incubation period. This lets us know the amount of photosensitive substance at every point of the cancerous tissue just before the radiation interval. It is assumed that the photosensitizer relaxation time is fast compared to the photosensitizer precursor diffusion time, $\tau_p << t$, and therefore the concentration of photoactive compound, is proportional with the instantaneous value of the precursor concentration. This value can be calculated by the equation 3, where ε_p is the yield of the conversion process and $\tau_{a\to p}$ the relaxation time of the photosensitizer precursor due to the generation of the photoactive compound[9].

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

The concentration of the photoactive compound accumulated in the target tissue at the end of the incubation period is used to calculate the photosensitizer absorption coefficient, μ_{a_PS} [cm^{-1}], at the beginning of the irradiation period taking into account the absorption cross section of the PpIX molecules, σ_{psa}, at the treatment wavelength as

$$\mu_{a\_PS} = \sigma_{psa} \cdot [S_0] \tag{4}$$

As it is shown later, this simple relationship between the photosensitizer absorption coefficient and the photosensitizer concentration, permits to study the evolution of this optical parameter as the photochemical reactions take place during PDT. It constitutes the basis to model the dynamic behavior of the photosensitizer absorption coefficient during the therapy by a differential equation, but also to study the influence of several parameters on it.

2.2 Modeling of the photosensitizer absorption coefficient during the photochemical reactions

Interaction of light with a photosensitizer at an appropriate wavelength produces an excited triplet state photosensitizer that interacts with ground state oxygen via two types of reactions, known as Type I and Type II. The Type II reaction is believed to be predominant and responsible for singlet oxygen production, which is considered as the cytotoxic element in charge of killing carcinogenic cells. When the ground state photosensitizer molecules absorb photons at an appropriate wavelength are promoted to the excited singlet state. Then they can decay back to the ground state emitting fluorescence or undergo intersystem crossing to produce the triplet photosensitizer state. Triplet photosensitizer state is quenched by ground state oxygen producing singlet oxygen or it can return to its ground sate emitting phosphorescence.

The photochemical reactions are characterized by means of a photochemical model[5, 10]. It is based in a stiff differential equations system (5 to 10) which takes into account the energetic transitions of the photosensitizer previously described and provides the temporal evolution of the molecular compounds involved in the Type II reaction.

$$\frac{d[S_0]}{dt} = -\nu\rho\sigma_{psa}[S_0] - kpb[^1O_2][S_0] + \frac{\eta_{10}}{\tau 1}[S_1] + \frac{\eta_{30}}{\tau 3}[T] + \frac{\alpha s}{\tau 3}[T][^3O_2] \tag{5}$$

$$\frac{d[S_1]}{dt} - \frac{1}{\tau 1}[S_1] + \nu\rho\sigma_{psa}[S_0] \tag{6}$$

$$\frac{d[T]}{dt} = -\frac{\eta_{30}}{\tau 3}[T] - \frac{\alpha s}{\tau 3}[T][^3O_2] + \frac{\eta_{13}}{\tau 1}[S_1] \tag{7}$$

$$\frac{d[^3O_2]}{dt} = -\frac{\alpha s}{\tau 3}[T][^3O_2] + \frac{\eta_0}{\tau 0}[^1O_2] + P \tag{8}$$

$$\frac{d[^1O_2]}{dt} = -kpb[S_0][^1O_2] - kcx[R][^1O_2] - ksc[C]_i[^1O_2] - \frac{\eta_0}{\tau_0}[^1O_2] + \frac{\alpha s}{\tau 3}[T][^3O_2] \tag{9}$$

$$\frac{d[R]}{dt} = -kcx[^1O_2][R] + U \tag{10}$$

In these equations, $[S_0]$ is the concentration of the photosensitizer in ground state, $[S_1]$ is the concentration of the photosensitizer in singlet excited state; $[T]$ is the concentration of photosensitizer in triplet excited state; $[^3O_2]$ is the concentration of oxygen in ground state; $[^1O_2]$ is the concentration of singlet oxygen; $[R]$ is the concentration of singlet oxygen receptors; $[C]_i$ is the scavengers concentration; $\tau 1$ is the relaxation time from state S_1 to S_0 ; $\tau 3$ is the relaxation time from state T to S_0 ; $\tau 0$ the relaxation time from state $^1O_2$ to $^3O_2$; η_{10} is the quantum yield of the transition from state S_1 to S_0; η_{13} is the quantum yield of the transition from S_1 to T; η_{30} is the quantum yield of T transition to S_0; η_0 is the quantum yield of $^1O_2$ transition to $^3O_2$; αs is the efficiency factor for energy transfer from T to $^3O_2$; *kpb* stands for the biomolecular photobleaching rate; *kcx* is the biomolecular cytotoxicity rate; *ksc* is the rate of reaction of with various oxygen scavengers; ν is light speed in tissue; ρ is the photon density present at a point; σ_{psa} is the absorption cross-section of S_0 molecules; P is the rate of oxygen diffusion and perfusion and U is the cell damage repair rate.

In this work we incorporated a new equation in the previous stiff differential equations system. This equation, described by the expression (11), represents the dynamic behavior of the photosensitizer absorption coefficient during PDT and its solution permits to obtain its temporal evolution. As it can be observed, it takes into account the absorption of photons by the ground state photosensitizer molecules, the photosensitizer photobleaching related to the singlet oxygen molecules produced and variations due to another photosensitizer transitions in different energetic states.

$$\frac{d\mu_{a\_PS}}{dt} = -\nu\rho\sigma_{psa}\mu_{a\_PS} - kpb[^1O_2]\mu_{a\_PS} + \frac{\eta_{10}}{\tau 1}\sigma_{psa}[S_1] + \frac{\eta_{30}}{\tau 3}\sigma_{psa}[T] + \frac{\alpha s}{\tau 3}\sigma_{psa}[T][^3O_2] \tag{11}$$

The solutions of the new stiff differential equations system (5 to 11) permit us to know the temporal evolution of the photosensitizer absorption coefficient along with the other molecular components involved in the photochemical reaction. The initial value for the photosensitizer absorption coefficient was obtained from the absorption cross section of the PpIX molecule and the concentration of photosensitizer accumulated in the target tissue at the end of its incubation period as it is shown in equation 4.

2.3 Optical radiation distribution

Optical modeling in a biological media implies dealing with an heterogeneous medium, which does not allow an analytic exact approach of the radiation pattern with Maxwell equations. The distribution of light in a three-dimensional tissue can be obtained by means of the Radiation Transport Theory (RTT)[1]. The model assumes that the scattering events are sufficiently numerous as to the light to be considered incoherent, in such a way that polarization or interference effects can be neglected. As a consequence, the basic parameter of light is the specific intensity $I(r,\hat{s})$, that is, the light power per unit area per unit solid angle. The radiation is expected to be at point $\vec{r}$, and to follow the direction $\hat{s}$. The scattering events are treated according to the scattering phase function $p(\hat{s}\cdot\hat{s}')$. Optical radiation comes from direction $\hat{s}'$ and is redirected to $\hat{s}$. The basic idea in order to write the differential radiation transport equation is that radiation from a particle attenuates due to absorption and scattering and also gains power because another particle can scatter light in the direction of the particle of interest. If there are no sources inside the tissue and a steady-state situation, this can be written:

$$\hat{s}\cdot\overline{\nabla} I(r,\hat{s}) = -(\mu_a + \mu_s) I(r,\hat{s}) + \frac{\mu_s}{4\pi}\int_{4\pi} p(\hat{s}\cdot\hat{s}') I(r,\hat{s}') d\Omega' \tag{14}$$

Regarding the radiation transport equation numerical analysis, the Monte Carlo method has demonstrated its applicability and accuracy, compared with exact solutions. The implementation of the Monte Carlo method applied to the RTT model used in this work is the one by Wang and Jacques[11, 12]. This implementation is multi-layered, with their borders always perpendicular to the laser beam. This is very useful because tissues usually can be divided in different strata. For the appropriate definition of the model, the characteristics and dimensions of each layer are required. The optical parameters needed are the index of refraction n, the absorption coefficient μ_a, the scattering coefficient μ_s and the anisotropy of scattering g. All these optical parameters are chosen according to the type of tissue and the wavelength of interest, and remain fixed regardless of their possible modification due to the effects of therapy. Furthermore, as far as we know the absorption coefficient used to get the optical radiation distribution in previous PDT modeling works, only took into account the tissue absorption but not its alteration due the photosensitizer molecules accumulated in it and neither its depletion during the photochemical reaction. In order to get a future more accurate optical radiation distribution modeling closer to a real PDT clinical application, we consider that the effective absorption coefficient at the beginning of the irradiation period is a consequence of not only the specific tissue absorption coefficient at the wavelength of treatment, but also of the photosensitizer molecules accumulated in the tissue during the incubation period previous to irradiation. The whole PDT model presented permits also to study the spatial evolution of the photosensitizer absorption coefficient at different times during the therapy. This last issue constitutes a first approach to develop new optical propagation approaches specifically designed for PDT which will take into account the influence of the photochemical effects on the optical parameters. The complexity of these future approaches falls basically on the need to integrate them in a dynamic system that allows an effective feedback between the optical and photochemical issues. From a clinical point of view, the main application of these future models will be the customized planning and real time monitoring of treatment. A rigorous choice of the model parameters in both applications will be of great importance to get accurate and realistic results which makes the modeling process complex due to the great amount of parameters of different nature involved.

3. RESULTS AND DISCUSSION

The PDT model described was applied to a dermatological disease treated with the topical photosensitizer Metvix® and superficial light application. Regarding the Metvix® cream photosensitizer, the clinical protocol only specifies that it is applied in a 1 mm thick layer on the affected area covering an extra 5 mm of healthy skin around the damaged area during an incubation period of 3 hours before radiation. Therefore in order to estimate the concentration of the PpIX precursor applied on the skin tumor as close as possible to a real case, we have taken into account the area of the pathology and MAL density per gram of Metvix® cream. Assuming a circular lesion of radius 1 cm, a MAL density of 160 mg per gram of Metvix® cream and the molecular mass of MAL, we calculated a MAL concentration on the pathology surface of $4.5031\cdot10^{20}$ cm^{-3}. The spatial and temporal diffusion of a topical photosensitizer precursor in the tissue sample and the photosensitizer endogeneously produced were obtained during the incubation period established in the clinical protocol. The corneal layer reduces the permeability of the skin, so that its value can be adjusted to characterize different skin conditions. In this case a damaged or reduced corneal layer caused by the skin lesion. As a consequence, the value of permeability, $K=10^{-6}$ m/s, was chosen greater than in the case of healthy skin with an intact cornea[9]. The diffusion coefficient through the epidermis and dermis was $0.69\cdot10^{-10}$ m^2/s, the relaxation time of the prodrug 24 hours, the yield of the conversion process 0.5, the relaxation time of the photosensitizer 84 ms and the relaxation time of the precursor due to the generation of the photosensitizer 25 hours[9, 13].

Once the concentration of MAL was known at each point, the accumulated concentration of active substance in the tissue during the incubation period was calculated. This lets us know the amount of photosensitive substance at every point of the cancerous tissue just before the radiation interval. It was assumed that the PpIX relaxation time is fast compared to the MAL diffusion time, $\tau_p << t$, and therefore the concentration of PpIX, is proportional to the instantaneous value of MAL concentration. The corneal layer blocked the diffusion to the deeper layers in the tissue during the first part of the photosensitizer incubation process and caused an uneven distribution of the photosensitizer in the tumor after the period of incubation.

The optical radiation distribution was obtained by means of the Monte Carlo method presented in the previous section. A cylindrical laser beam with a radius of 0.3 cm perpendicular to the tissue sample was used to deliver and irradiance of 100 mW/cm^2. The radiation time was 10 minutes. The tissue geometry proposed was composed of two layers. The upper one was a basal cell carcinoma (BCC) tumor (3 mm) that lied on healthy tissue. The tissue optical properties[14] used at the excitation wavelength (635 nm) for the tumor were μ_a=1.5 cm^{-1}, μ_s=104.76 cm^{-1}, g=0.79 and n=1.5 whereas the healthy tissue beneath the tumor was considered muscle with an index of refraction of 1.37.

Literature related to well known photosensitizers of the porphyrins family was employed to assign the parameters values related to the photosensitizer PpIX when they were not available[15]. Thus the initial photosensitizer absorption coefficient used as initial condition in the photochemical model (5-11) was obtained by means of equation 4, taking into account the previously obtained inhomogeneous photosensitizer concentration and an absorption cross-section of the PpIX, σ_{psa} = $0.37 \cdot 10^{-15}$ cm^2 at 635 nm, which was derived from a study of the cellular photosensitizing properties of PpIX carried out in a transformed murine keratinocyte cell line[16]. Due to the fact that MAL is a derivative of 5-aminolevulinic acid, the relaxation time from singlet excited state to ground state S_1 to S_0 was set to 7.4 ns as reported earlier from fluorescence measurements in cells incubated with 5-aminolevulinic acid induced PpIX[17]. The triplet state lifetime in vivo in skin (τ3) was set to 26 μs and the relaxation time of $^1O_2$ to $^3O_2$ to 0.04 μs, [18]. Quantum yield transitions between different energetic states were adopted to be similar to those previously considered for the photosensitizer Photofrin® η_{10}=0.2, η_{30}=0.3, η_0=0.3 and η_{13}=0.8 as well as biomolecular photobleaching, citotoxicity and scavenging rates that were set to $2 \cdot 10^{-10}$ cm^3/s^{-1}, $2 \cdot 10^{-9}$ cm^3/s^{-1} and $1 \cdot 10^{-9}$ cm^3/s^{-1}, respectively[10]. When the optical irradiation period starts, there are not molecules of photosensitizer in excited state, so the initial concentration of S_1 and T are 0 cm^{-3}. In the same way singlet oxygen molecules have not yet been produced and their initial concentration is 0 cm^{-3}. The initial concentration of cellular oxygen was set to $5 \cdot 10^{17}$ cm^{-3}, and diffusion and perfusion rates to $1 \cdot 10^{12}$ cm$^{-3} \cdot$s^{-1}, [10]. The oxygen depletion due to the photochemical reaction consumption is described by the first left term in equation 8, while its reposition is taken into account by the rest of the terms. The last one is the rate of oxygen diffusion and perfusion. The initial concentration of intracellular molecular singlet oxygen receptors was $5 \cdot 10^{17}$ cm^{-3}, the scavenger concentration was $1 \cdot 10^3$ cm^{-3} and the cell damage repair rate $2.6 \cdot 10^{12}$ cm$^{-3} \cdot$s^{-1}, [10].

The solutions of the stiff differential equations system employed were obtained by means of a differential equation solver within the Matlab® platform. In order to obtain coherent results, we had to adjust relative and absolute error tolerances. These solutions provided the temporal evolution of the molecular concentrations of the compounds involved in a Type II reaction everywhere in the tissue sample. Furthermore the incorporation of the equation (11) to the photochemical model provided the spatial evolution of the photosensitizer absorption coefficient taking into account the excitation photons absorption and its depletion due to the photosensitizer photobleaching and other energetic transitions. The results are shown in Figure 1, that shows the spatial variation of the photosensitizer absorption coefficient at different temporal instants (a) t=$1 \cdot 10^{-8}$ s, b) 6 s, c) 300 s y d) 600 s) during PDT for the conditions previously specified. As it can be observed, the fast photobleaching of the photosensitizer has a great influence in the photosensitizer absorption coefficient making it decrease as the therapy progresses and therefore diminishing its effect on the optical propagation. This effect is observed first in the most superficial parts of the tumor and continues expanding deeper in the tissue with time. Thus when only $1 \cdot 10^{-8}$ seconds (Fig. 1a)) have passed since the irradiation began, the photosensitizer absorption coefficient is maximum due to the fact that singlet oxygen molecules have not yet been produced and therefore the photobleaching effects have not been noticed yet. When 6 seconds have passed, these effects become visible and more pronounced as long as the irradiation time progresses as it can be observed at half treatment (300 s) (Fig. 1 c)) and at the end of the irradiation (600 s) (Fig. 1d)). Comparing the photosensitizer absorption coefficient temporal evolution, it can be seen that as the photobleaching increases the biggest photosensitizer absorption coefficient is localized in the deeper areas of the tumor where the therapy effects are produced later than in the superficial ones. Therefore it is expected that these changes in the photosensitizer absorption coefficient during the treatment, affect to the light propagation in the tissue as the treatment progresses and as a consequence in the final treatment effects. These results indicate that the modeling of the light propagation in a tissue subjected to PDT should consider the photochemical aspects underlying the photodynamic process to get results closer to the real clinical application.

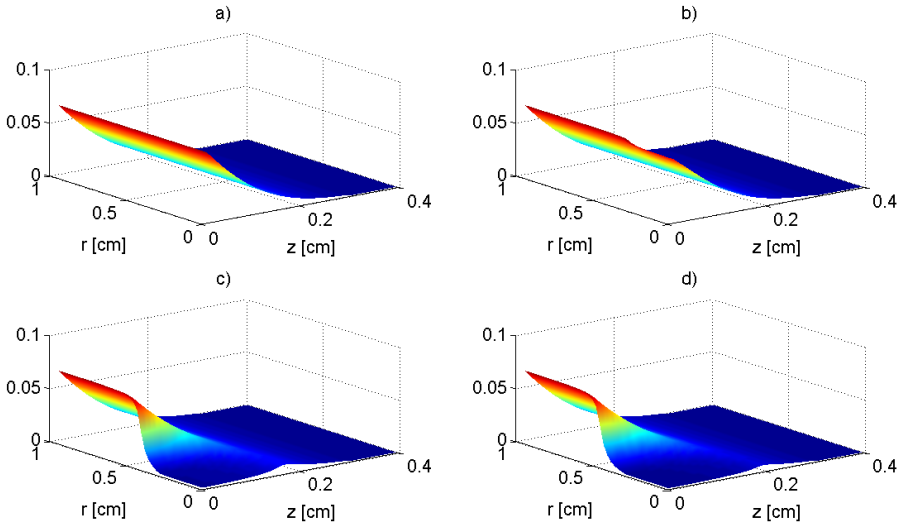

Figure 1. Photosensitizer absorption coefficient [cm^{-1}] at a) $t = 1 \cdot 10^{-8}$ s, b) t = 6 s, c) t = 300 s and d) t = 600 s vs. z (depth in the tissue) and r (distance to the center of the light beam).

4. CONCLUSIONS

The development of custom clinical protocols to adapt current stiff PDT dosimetry to new personalized and dynamic treatments implies an accurate planning and therapy monitoring. For this purpose the modeling of the whole photodynamic process will constitute a valuable tool to estimate the treatment outcome before its application and to study the influence of the parameters involved. Several attempts have been made in this way although the influence of the photosensitizer distribution on the optical parameters has not been taken into account until this moment. We have presented a first approach to predict the spatial-temporal variation of the absorption coefficient during the photodynamic process taking into account the photobleaching of the photosensitizer. The PDT model employed in the present work also takes into account the optical radiation distribution, the non-homogeneous topical photosensitizer distribution and the time-dependent evolution of molecular components involved in the photochemical interactions. The model was applied to a basal cell carcinoma taking into account its optical properties to obtain the distribution of the optical propagation and its geometric characteristics to calculate the photosensitizer accumulation in the tumor during the drug incubation period. The temporal and spatial evolution of the photosensitizer absorption coefficient was obtained and showed a quick variation as a consequence of the photosensitizer degradation, starting from the outer areas of the tumor and propagating to the deeper ones as the treatment progressed. Therefore it is expected that these changes in the photosensitizer absorption coefficient affect the light propagation in the tissue during the treatment and as a consequence in the final therapeutic effects. These results indicate that the modeling of the light propagation in a tissue subjected to PDT should consider the photochemical aspects underlying the photodynamic process to get a proper optical radiation distribution and results closer to the real clinical application.

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