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Photochemical Approach of Photodynamic Therapy Applied to Skin

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***Abstract*—Photodynamic Therapy (PDT) is a recent treatment modality that allows malignant tissue destruction. The technique provides a localized effect and good cosmetic results. The application of PDT is based on the inoculation of a photosensitizer and the posterior irradiation by an optical source. This radiation chemically activates the drug and provokes reactions that lead to tissue necrosis. Nowadays there are fixed clinical PDT protocols that make use of a particular optical dose and photosensitizer amount. These parameters are independent of the patient and the lesion. In this work we present a PDT model that tries to predict the effect of the treatment on the tissue. The 3D optical propagation of radiation is calculated by means of the Radiation Transport Theory (RTT) model, solved via a Monte Carlo numerical model. Once the optical energy is obtained, a complex photochemical model is employed. This model takes into account the electronic transitions between molecular levels and particles concentrations. The data obtained allow us to estimate the destroyed area. The optical power of the source, the exposition time and the optochemical characteristics of the tissue can be varied. This implies that these parameters could be adjusted to the particular pathology we are dealing with. As a consequence, the treatment would be more efficient. We apply the model to the skin, due to the fact that PDT is commonly applied on it.**

I. Introduction

BIOMEDICAL optics provides practitioners with new and powerful techniques for biological tissues characterization and for treatment applications [1]. Regarding optical treatment, two of the most important optical techniques are Thermotherapy (in which a slight temperature increase provokes an improvement process in the pathological tissue), and Photodynamic Therapy (PDT). The aim of Photodynamic Therapy is malignant tissue destruction. In particular, the most usual application of PDT involves neoplastic tissues. The key of PDT lies in the photosensitizer, a substance that is inoculated and has the property that it is selectively accumulated in the region that is intended to be suppressed [2]. Once the photosensitizer is fixed to the problematic tissue, it has to be activated by means of a radiation applied to the area of interest, and subsequently giving rise to a biochemical process that produces the selective destructive effect. The amount of tissue destroyed will depend on both the properties of the photosensitizer and of the light source. On the one hand, the substance inoculated in the tissue, its reactive characteristics and its spatial distribution are different aspects of the photosensitizer factors affecting the final result of PDT. On the other hand, some specific properties of the optical source used for irradiation have also a direct impact in tissue destruction, namely: optical irradiation, wavelength and exposition time. It is necessary to emphasize that all these aspects have to be taken into account as long as one of the main aspects of the application of this technique lies in the accurate delimitation of the volume of tissue affected. Such delimitation is essential in order to restrict the treatment to the pathological tissue and protect adjacent tissues, avoiding any undesired collateral effect.

In this work a PDT model applied to skin disorders is presented. PDT principles are described in section 2. Section 3 describes the 3D optical propagation of radiation by means of the Radiation Transport Theory via a Monte Carlo numerical approach. The spatial optical energy is introduced in a photochemical model for the PDT process applied to skin diseases. The different molecular reactions are modelled by means of a differential equations system. This system is solved via a numerical method, taking into account its stiff nature. This is shown in section 4. Prior predictive analysis was based on a simplified model for the photochemical processes involved [3,4]. The model is applied to the skin and some results appear in the next section. The evolution of the PDT process can be predicted for different optical source parameters, and so the treatment effect could be known a priori.

II. Photodynamic Therapy

Photodynamic Therapy is an optical technique for malignant tissue destruction. It is based on the use of a chromophore that catalyzes the reaction known as photosensitized oxidation. Firstly, a photosensitizer is applied to the tissue, and its biochemical properties result in a location in malignant cells, remaining in them and leaving the healthy cells unmarked after a selective deposition process. The photosensitizer is not dangerous by itself, but when optically excited it encourages photochemical and photobiological processes that lead to a lethal effect in tumoral tissues. Therefore, the next step is to apply a light

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source to the tissue with the aim to excite the photosensitizer. The characteristics of the optical irradiation, like wavelength, have to be appropriately adjusted depending on the specific photosensitizer characteristics in terms of absorption response. As a consequence, once the photosensitizer is irradiated, it suffers an excitation process. As it goes back to the ground state, the decays activate the molecular oxygen and reactive oxygen species (ROS) are created. These species are greatly cytotoxic, and as a consequence they provoke an irreversible oxidation of the essential structures of the involved cells. It should be remarked that the oxygen is absolutely essential for these photochemical reactions to take place. The direct consequence of this statement is that cellular necrosis by means of this process cannot be produced in anoxic conditions [5]. Although the main application of PDT is the destruction of cancerous tissue, it can also be employed in other medical procedures, like dermatology, ophthalmology (Age-related Macular Degeneration), molecular biology or even aesthetics [6].

The use of PDT in dermatology presents several advantages in relation to conventional techniques. First of all, it is a non-invasive technique. Its high specificity and selectivity enable that healthy tissue is unaffected. Secondly, it is easily tolerated by patients. In this sense, in case a slight pain would appear in the treated area, it could be suppressed by the application of air or cold water. Thirdly, various lesions can be treated in the same session, and the treatment can be repeated as many times as necessary. As well as this, no scars are produced, so the cosmetic result is usually excellent. Finally, the simplicity of the procedure makes that no special skills of the practitioner are required, and difficult lesions (multiple or extended lesions) can be treated. Collateral effects are slight, temporary and limited to the treated area. As a disadvantage of PDT, it should be noted the inability to assess the cure of tumour by histological confirmation. Another disadvantage is that the procedure is slow, because the treatment requires preparation of the affected area and the patient has to be seen again after three hours for a second illumination. PDT is not indicated in case of hypersensibility to the photosensitizer or in morpheiphorm basocellular epitheliomas.

III. Monte Carlo Optical Model

There are different optical models for using in biological tissue. Modelling a biological tissue implies dealing with an heterogeneous medium, which does not allow an analytic exact approach of the radiation pattern with Maxwell equations. For the problem we are dealing with, the distribution of light in a three-dimensional tissue must be obtained. This objective is reached 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, $I(\vec{r},\hat{s},t)$ ($W/m^2 sr$), 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 $\hat{s}$ direction. The scattering events are treated according to the scattering phase function, $p(\hat{s},\hat{s}')$, which contains the probabilities of light to be scattered in the different directions. Light 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. This, with no sources inside the tissue and a steady-state situation, can be written as

$$\hat{s}\cdot\overline{\nabla}I(r,\hat{s}) = -(\mu_a+\mu_s)I(r,\hat{s}) + \frac{\mu_a+\mu_s}{4\pi}\int_{4\pi} p(\hat{s}\cdot\hat{s}')I(r,\hat{s}')\,d\Omega' \quad (1)$$

where μ_a is the absorption coefficient, μ_s is the scattering coefficient, Ω refers to the solid angle and $Q(r(t),\hat{s},t)$ represents a source placed at the point of interest.

Numerical analysis has been widely applied to a great variety of problems governed by differential equations. In the particular topic of the radiation transport equation, the Monte Carlo method has demonstrated its applicability and accuracy, compared with exact solutions. Perhaps the most used implementation of the Monte Carlo method applied to the RTT model is the one by Wang and Jacques [7]. They programmed the Monte Carlo method in standard C. The key point is the inclusion of the random character on a computer, by means of a mathematical probability analysis, in such a way that numbers with any probability distribution can be obtained from numbers that follow a uniform distribution between 0 and 1. Light is treated as a sequence of photons, whose number is intended to be representative of the accuracy of the solution obtained. One photon is launched and its trajectory, affected by scattering, and loss of energy are calculated, while the absorption in each point is stored. Cylindrical symmetry is assumed, because laser beams usually show this kind of symmetry, so in fact the data can be interpreted as coming from a 3-D analysis. The complete tissue is divided in a two-dimensional grid in the r and z directions of the cylindrical coordinates system. As usual, more accurate results require a smaller grid, but the need of a reduced time of computation imposes a limit. The Monte Carlo program assumes that the optical beam is infinitely narrow, and that it has perpendicular incidence. The second assumption is reasonable, but the former can provoke serious disappointments with the reality, specially if the dimensions of the optical spot and the tissue are of the same order. In order to correct this limitation, another program by the same

authors [8] implements the convolution of the results. In this way, the solution of the Monte Carlo analysis can be later transformed for taking into account cylindrical or gaussian geometry of the laser beam.

This implementation of the Monte Carlo model is also multi-layered, so it is possible to define several layers of different materials, with their borders always perpendicular to the laser beam, which is very useful due to 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. This last parameter is called average cosine of scatter (dimensionless), and is related with the scattering phase function. The average cosine of scatter gives an idea about the probability of being scattered in a particular direction. For instance, $g = 0$ implies that all directions all equally probable. If $g > 0$ the radiation tends to be scattered forward, and vice versa. The albedo tries to illustrate the predominance of absorption or scattering in a particular tissue.

IV. Photochemical Model

Complex reactions take place during Photodynamic Therapy, which involves a lot of parameters. The predictions obtained are a function of the parameter values and the model simplifications assumed. Nevertheless, the results allow us to interpret the process evolution and to establish certain parameter limits. The photochemical model is based on a differential equations system [9], (1) to (6). It takes into account the transitions between states of the particles involved, like the photosensitizer or the oxygen.

$$\frac{d[S_0]}{dt} = -v\rho\sigma_{psa}[S_0] - kpb[^1O_2][S_0] + \frac{\eta_{10}}{\tau 1}[S_1] + \frac{\eta_{30}}{\tau 3}[T] + \frac{\alpha s}{\tau 3}[T][^3O_2] \quad (2)$$

$$\frac{d[S_1]}{dt} = -\frac{1}{\tau 1}[S_1] + v\rho\sigma_{psa}[S_0] \quad (3)$$

$$\frac{d[T]}{dt} = -\frac{\eta_{30}}{\tau 3}[T] - \frac{\alpha s}{\tau 3}[T][^3O_2] + \frac{\eta_{13}}{\tau 1}[S_1] \quad (4)$$

$$\frac{d[^3O_2]}{dt} = -\frac{\alpha s}{\tau 3}[T][^3O_2] + \frac{\eta_0}{\tau 0}[^1O_2] + P \quad (5)$$

$$\frac{d[^1O_2]}{dt} = -kpb[S_0][^1O_2] - kcx[R][^1O_2] - ksc[C]i[^1O_2] - \frac{\eta_0}{\tau 0}[^1O_2] + \frac{\alpha s}{\tau 3}[T][^3O_2] \quad (6)$$

$$\frac{d[R]}{dt} = -kcx[^1O_2][R] + U \quad (7)$$

In these equations, $[S_1]$ is the concentration of the photosensitizer in singlet excited state; $[T]$ is the concentration of photosensitizer in triplet excited state; $[^3O_2]$ the concentration of oxygen in ground state; $[^1O_2]$ is the concentration of singlet oxygen; $[R]$ the concentration of singlet oxygen receptors; $[C]i$ is the scavenger concentration; τ_1 is the relaxation time from state S_1 to S_0; τ_3 is the relaxation time from state T to S_0; τ_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 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 $^3O_2$; α_s 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 $^1O_2$ with various oxygen scavengers; ν is light speed in tissue; ρ is the photon density; 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.

The stiff differential equations system was solved by means of a differential equation solver (*ode15s*) within the Matlab® platform. In order to obtain coherent results, we had to adjust relative and absolute error tolerances and solve on a time interval from 0 to 4000 s with an initial condition vector at time 0.

V. Results

The complete photochemical model was implemented for the particular case of PDT applied to the skin. The results obtained represent a graphical description of the different concentrations of photosensitizer, oxygen and singlet oxygen receptors for every point and temporal instant in the tissue sample.

We show the results obtained using an incident irradiance of 50 mW/cm² in three points of the tissue sample. In Fig.1 are represented the photochemical reactions evolution in the tissue surface at a distant point of the laser beam.

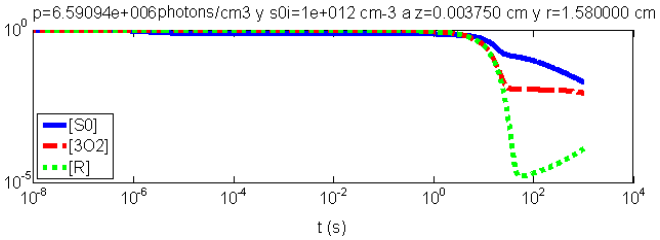

Fig. 1. This graphic describes the time dependence of the concentrations of photosensitizer in ground, of oxygen in ground state, and of singlet oxygen receptors for Io=50 mW/cm² in tissue surface.

In Fig.2 the same evolution in a middle depth point in the tissue sample can be observed.

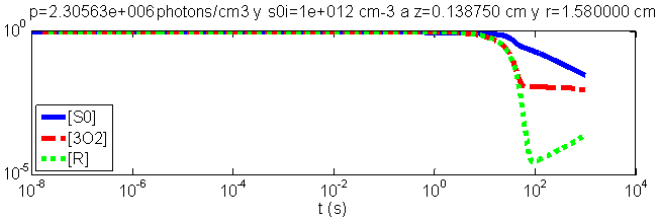

Fig. 2. This graphic describes the time dependence of the concentrations of photosensitizer in ground state, of oxygen in ground state, and of singlet oxygen receptors for Io=50 mW/cm² in a middle depth point in the tissue sample.

Finally we present the photochemical reactions evolution in a deep point of the tissue sample.

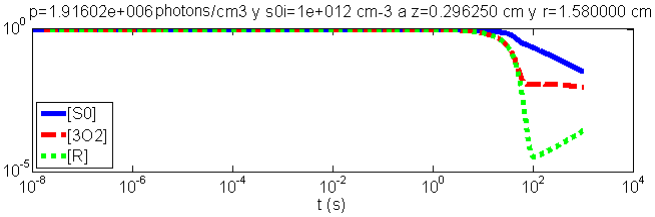

Fig. 3. This graphic describes the time dependence of the concentrations of photosensitizer in ground state, of oxygen in ground state, and of singlet oxygen receptors for Io=50 mW/cm² in a deep point in the tissue sample.

As it can be observed in the figures showed, the concentration of ground state molecules of photosensitizer, oxygen in ground state and receptors vary slowly in response to the activation light. It is supposed that this minimum in receptors concentration produces the desired cytotoxic effect, so we have made several simulations in order to adjust the optimal drug and light dose which will produce this effect in the shortest period of irradiation and for the largest depth of action in cancerous tissues. We can also observe how the time to achieve the maximum cytotoxic effect is increased with depth.

VI. Conclusions

Photodynamic Therapy is a treatment modality that presents advantages over conventional techniques, like the non-contact character, the localized destructive effect or the good cosmetic results. The present application of the therapy is based on fixed protocols that do not take into account the particularities of the patient.

A complete model of the PDT process was presented. First a numerical Monte Carlo model for light propagation in tissue was described. A photochemical model, that uses the Monte Carlo data, was used to obtain results on the skin. The different concentrations of the elements show the effect of the treatment.

The variation of the optical source and optochemical properties of the tissue in the model allows the prediction of the PDT result. In this way, the therapy could be optimized for the particular pathology treated.

This work constitutes a first approach to model how the different components involved in a photodynamic reaction vary. Therefore these first results must be interpreted carefully due to the great amount of parameters involved in these complex photoreactions. Subsequently future research works are required to improve the results obtained and to continue developing new accurate models.

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