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Investigation of thermal distribution for pulsed laser radiation in cancer treatment with nanoparticle-mediated hyperthermia

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ABSTRACT

In this paper, we have simulated the efficacy of gold/gold sulfide (GGS) nanoshells in NIR laser hyperthermia to achieve effective targeting for tumor photothermal therapy. The problem statement takes into account the heat transfer with the blood perfusion through capillaries, and pulsed laser irradiation during the hyperthermia. Although previous researchers have used short laser pulses (nanosecond and less), in order to prevent heat leakage to the neighbor tissues, we have examined the effect of millisecond pulses, as the extent of the target volume to which hyperthermia is induced is usually larger and also the lasers with this specification are more available. A tumor with surrounding tissue was simulated in COMSOL software (a finite element analysis, solver and simulation software) and also in a phantom made of agarose and intralipid. The tumor was irradiated by 10, 20 and 30 laser pulses with durations of 15, 50 and 200 ms and fluences of 20, 40 and 60 J/cm^2. Experimental tests performed on a phantom prove the ability of the applied numerical model to capture the temperature distribution in the target tissue. We have shown that our simulation permits prediction of treatment outcome from computation of thermal distribution within the tumor during laser hyperthermia using GGS nanoshells and millisecond pulsed laser irradiation. The advantage of this simulation is its simplicity as well as its accuracy. Although, to develop the model completely for a given organ and application, all the parameters should be estimated based on a real vasculature of the organ, physiological conditions, and expected variation in those physiological conditions for that application in the organ.

1. Introduction

Heat has long been utilized as a therapeutic tool in medicine. Laser-induced thermotherapy aims at achieving the local destruction of lesions, relying on the conversion of the light absorbed by the tissue into heat (Sturesson, 1994). Hyperthermia is applied as an adjuvant technique for cancer treatment. In hyperthermia, the targeted tissue must be elevated to temperatures in the range of 46–50 °C to cause cancerous cell death due to enzymatic processes (Lopez, 2006). Laser heating can result in both tumor necrosis (and possibly apoptosis) and in accelerated tumor growth, depending on the accuracy of heating and on the rise in tumor temperature on illumination with laser light. Specifically, heating up to 39–45 °C may lead to the acceleration of biological reactions accompanied by the production of shock-heating proteins and by intense growth of the tumor. Temperature rise to 46–50 °C is accepted as optimal for hyperthermia treatment (Terentyuk et al., 2009).

One challenge in hyperthermia treatment is localization of heat in the target area to destroy cancerous cells without significantly affecting the surrounding healthy tissue. Recent developments of nanoparticle technology and its application in hyperthermia therapies enable more selective heating and lower thermal doses to be employed to achieve a more precise control of the thermal energy delivered to the tumor region. Nanoparticle mediated hyperthermia results in more effective tumor eradication and minimal destruction of surrounding healthy tissue (Feng et al., 2005). Many studies were focused on different aspects of the laser radiation in various human tissues with embedded nanoparticles (Khlebtsov et al., 2006; Maksimova et al., 2007; Khlebtsov and Dykhman, 2010; Huang and El-Sayed, 2010; Rupesh et al., 2014; Sanjeev et al., 2014).

In this study, the distribution of temperature under exposing gold nanoparticle labeled cells to NIR laser radiation is determined by simulating the absorption of light by nanoparticles acting as point-wise local heat sources, and by thermal diffusion over

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surrounding tissues, in order to predict the feasibility of inducing hyperthermia by the millisecond laser pulses and determining the temperature difference between the tumor (with GGS) and its surrounding tissues (without GGS). Also the effects of duration and fluence of the laser pulses were evaluated on the temperature variation profile. Although previous researchers have used nanosecond laser pulses, in order to prevent heat leakage to the neighbor tissues, we have examined the effect of millisecond pulses which are more available. The main aim of this research is to study this objective that in order to achieve hyperthermic condition, low fluence and/or long duration should be selected.

In order to achieve precise results, an accurate heat transfer model must be developed which considers complexities in the heat tissue interactions. This model must be coupled to a good heat source model. It is well known that soft human tissues are semi-transparent for visible and near-infrared radiation (NIR) (Dombrovsky et al., 2011). Of course, various tissues have specific optical properties but the most wide therapeutic optical window considered in the literature is a wavelength range from 600 to 1400 nm (Mobley and Vo-Dinh, 2003). Readers can find data for optical properties of tissues of various human and animal organs in the literature (Dombrovsky et al., 2011; Mobley and Vo-Dinh, 2003; Duck, 1990; Feng et al., 2009). In addition to the absorption coefficient, the data for the scattering coefficient, asymmetry factor of scattering, and index of refraction are usually given. It should be noted that, optical properties of tissues are very specific, patient dependent, and there is a considerable uncertainty in the experimental results even for the same type of tumors. This challenge leads to a limited accuracy of the radiative transfer predictions, which are important for any computational modeling of the photothermal therapy process (Dombrovsky et al., 2011).

In this study, we consider a special class of nanoparticles called nanoshells, which can act as intense infrared absorbers increasing the thermal deposition of laser energy into the tumor. In particular, nanoshells provide a potential means to (a) enhance the delivery of laser-induced thermal energy via distributing the heat source from the fiber to the surrounding vasculature and/or, (b) provide a highly conformal and targeted approach to laser-induced thermal therapy in which normal tissue is spared and tumor tissue is ablated with a high level of specificity (Baer et al., 2004; Lin et al., 2004). Typically, gold nanoshells (GNSs) consist of a concentric spherical dielectric (silica) core and a thin metal coating (Au) shell. The average diameter of nanoshells is usually in the range of 110–120 nm and has been shown to be effective mediated agents to control the temperature field (Baer et al., 2004; Lin et al., 2004). Nanoshells possess a highly tunable plasmon resonance which determines the particle's scattering and absorbing properties. The plasmon resonance, one of the nanoshell's optical properties, can be tuned across a broad range of the light spectrum from the ultra-violet to the infrared by controlling the ratio between the radius of the core and the thickness of the shell layer (Baer et al., 2004; Lin et al., 2004).

As the optimal design of NIR absorber gold nanoshells requires difficult and expensive syntheses, we utilized gold/gold sulfide (GGS) nanoshells which can be synthesized easily with considered dimensions. The ability of GGS nanoshells can be exploited for the targeted laser therapy of a cancer to convert the absorbed light into the localized heat. These nanoparticles strongly absorb NIR wavelengths of light which deeply penetrate into the tissue. A promising alternative to conventional treatment modalities, nanoparticle-assisted photothermal therapy, is minimally invasive, highly effective, and anticipated to have limited side effects. Thus, effective targeting of nanoshell bioconjugates specifically to cancer cells, combined with the high absorption cross-section of GGS nanoshells in the NIR region, generates increased temperatures sufficient to produce irreversible tumor cell damage while keeping laser energy at a lower level so that cells outside of the target region are minimally damaged (Hirsch et al., 2003; Oldenburg et al., 1999).

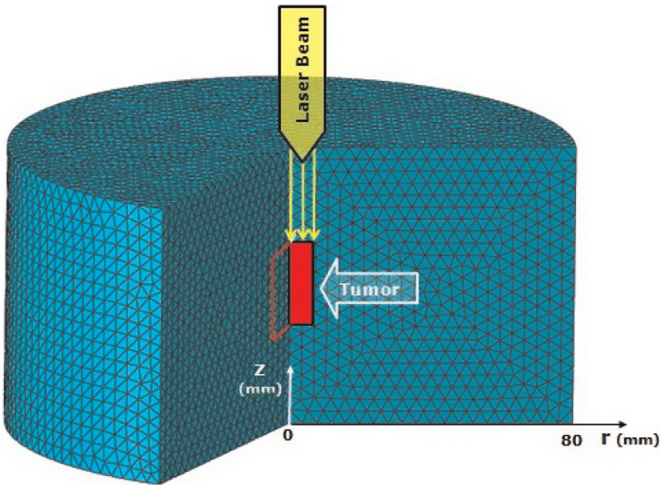

Fig. 1. Three-dimensional view of the healthy tissue and tumor as simulated by COMSOL. The large cylinder shows the healthy tissue, and the small internal cylinder located exactly in the middle of the larger one, shows the tumor. The tumor is located at a depth of 30 mm from the surface of the skin.

2. Material and methods

2.1. Mathematical formulation of the problem

Optimal design of laser radiation protocols for the nanoparticle mediated hyperthermia therapy requires the reliable modeling of optical properties of the tissue and nanoparticles, the bioheat transfer, and the cell damage. In the following subsection, we briefly describe the models and parameter values used in our study.

The mathematical representation of the temperature distribution in the tissue incorporates both the Pennes bioheat equation for thermal effects of the local blood perfusion and an expression for the laser energy as a thermal source (Feng et al., 2005, 2009; Pennes, 1948).

$$\rho c\frac{dT}{dt} = \nabla(k\nabla T) + \omega_b\rho_b c_b(T_a - T) + Q \quad (1)$$

Where

$$Q = \mu_{atot}\Phi = 3P\mu_{atot}\mu_{tr}\exp[-\mu_{eff}X - X_0]/4\pi X - X_0$$

Q is the rate of the absorbed laser energy per unit volume distributed within the tissue. , c, and k are the density, specific heat and thermal conductivity of the tissue, respectively. The blood perfusion rate, specific heat of the blood, arterial blood temperature, and fluence are defined respectively as ω_b, c_b, T_a and Φ. The notations μ_{atot}, μ_{tr}, and μ_{eff} represent the total absorption, transport attenuation, and effective irradiation coefficients, respectively. P is the power of the laser.

Table 1
Thermal properties employed in the model (He et al., 2006; Anvari et al., 1994).

Parameter	Tissue	Blood	Tumor	Units
Density	1050	1100	1050	$kg\ m^{-3}$
Specific heat	3770	3300	3770	$J\ kg^{-1}\ K^{-1}$
Thermal conductivity	0.48	0.45	0.48	$W\ m^{-1}\ K^{-1}$