Laser-Induced Thermal Treatment of Superficial Human Tumors: An Advanced Heating Strategy and Non-Arrhenius Law for Living Tissues

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The most interesting, but insufficiently known results obtained by the author in modeling laser-induced hyperthermia of human tumors are discussed. It is important that the traditional equation for the local bio-heat transfer does not work in superficial layers of the body. It is shown also that the classical Arrhenius law is not applicable to living tissues because of the tissue regeneration due to oxygen supplied by the arterial blood. The latter is one of the main reasons of the suggested strategy of laser heating of tumors in the therapeutic window of semitransparency when the tumor asphyxiation is considered as one of important weapons against the cancer. The other advantages of this advanced strategy of a soft thermal treatment (in few of sessions), which is painless for patients, are discussed as well. Some features of modeling various heat transfer modes are also considered. The best choice between the simplest differential models for the radiative transfer calculations is dependent of the particular problem statement. The known finite-difference or finite element algorithms can be preferable in solving transient heat transfer problems. As a rule, it depends on the shape of the computational region. It is expected that this paper will help the colleagues to overcome some typical weaknesses of computational modeling of infrared photothermal treatment of superficial tumors.

Keywords: laser heating, hyperthermia, superficial tumors, photothermal treatment, radiative transfer, advanced heating strategy, non-Arrhenius kinetics, computational modeling

INTRODUCTION

Hyperthermia or thermal therapy, most likely, is the oldest method of treating superficial human tumors (there is documentary evidence of the use of this method in ancient Egypt around 3000 BC). With the invention of modern lasers, this method, sometimes used in combination with chemotherapy and ionizing radiation therapy (van der Zee, 2002; Camerin et al., 2005; Datta et al., 2015; Mallory et al., 2016; Peeken et al., 2017), has been fundamentally improved and continues to be successfully applied in medical practice. The essence of local tumor hyperthermia is that cancer cells are destroyed even with slight (up to 42–44°C), but prolonged overheating, while under similar and even stronger thermal conditions the healthy cells can be self-regenerated (Yarmolenko et al., 2011; Spichka et al., 2019).

The intensive development of modern technologies has led to the use of gold and composite nanoparticles in laser hyperthermia (mainly for the treatment of superficial tumors) (Huang and

El-Sayed, 2010; Chatterjee et al., 2011; Bayazitoglu et al., 2013; Jague et al., 2014; Abadeer and Murphy, 2016; Kaur et al., 2016; Bucharskaya et al., 2018; Dykman and Khlebtsov, 2019; Vines et al., 2019). The implementation of such particles into biological tissues leads to a significant increase in the local absorption coefficient in one or another part of the therapeutic semitransparency window, which covers the wavelength range from about 0.6 to 1.4 μm (Cheong et al., 1990; Duck, 1990; Mobley and Vo-Dinh, 2003; Tuchin, 2007; Bashkatov et al., 2011; Jacques, 2013) and allows one to act on tissues at a certain depth under the irradiated body surface.

The possibility of using short-pulse lasers has led to the development of alternative methods of laser-induced treatment and to new difficulties in modeling processes in biological tissues, especially when nanoparticles are embedded in tissues (Jaunich et al., 2008; Muthukumaran and Mishra, 2008; Liu and Hsu, 2008; Bhuvaneswari and Wu, 2009; Ruan et al., 2010; Mishra et al., 2012; Zhang et al., 2013; Browmik et al., 2014; Randrianalisoa et al., 2014; Yakovlev et al., 2019). At the same time, a number of methodological issues that arise even with the use of continuous-wave lasers and without nanoparticles remain insufficiently clarified. As a result, even in recent publications there are physical errors in the formulation of the heat transfer problem and also not reasonable choice of the method for calculating the radiative transfer. Moreover, the kinetic models of thermal tissue injury ignore the continuous regeneration of living tissue due to oxygen supplied by erythrocytes of the arterial blood. These disadvantages not only may lead to significant errors in the calculations, but also do not make it possible to choose the right strategy for combating superficial cancerous tumors.

In this regard, the author considers the objective of the present work in a well-grounded and understandable presentation of key physical issues using the example of the most technically simple model of laser-induced hyperthermia.

TRANSPORT APPROXIMATION AND DIFFERENTIAL MODELS

The radiative transfer in biological tissues has the following features that are important for the rational choice of an appropriate method for solving the problem:

1 In the therapeutic window of semitransparency, the scattering of radiation by numerous structural elements of each biological cell with size comparable with the radiation wavelength is much greater than the absorption of radiation (e.g. Mobley and Vo-Dinh, 2003).
2 To calculate the temperature of biological tissue, it is necessary to know the power field of the radiation absorbed in the medium, while the angular distribution of the radiation intensity does not matter.

The first of these circumstances means that the incident radiation undergoes multiple scattering. In problems of this type, the details of the phase function of single scattering are not important, and the simplest transport approximation is quite sufficient. According to this approximation, the scattering function is replaced by a sum of the isotropic component and the term describing the peak of forward scattering. In this case, the general radiative transfer equation (Howell et al., 2021; Modest and Mazumder, 2021) is greatly simplified and has the same form as that for the hypothetical isotropic scattering. The transport approximation, first proposed for problems of neutron transport (Davison, 1957; Pomraning, 1965; Sanchez and McCormick, 1982), is widely used for radiative heat transfer in scattering media by (Dombrovsky, 1996a, Dombrovsky, 1996b, Dombrovsky, 2012, Dombrovsky, 2016, Dombrovsky, 2019) and by Dombrovsky and Baillis (2010), as well as for radiative transfer in biological tissues (Tuchin, 2007; Kienle et al., 2007; Sandell and Zhu, 2011; Jacques, 2013; Dombrovsky et al., 2011, Dombrovsky et al., 2012, Dombrovsky et al., 2013, Dombrovsky et al., 2015, Eisel et al., 2018). Note that researchers dealing with the optical properties of biological tissues talk about equivalent isotropic scattering and use the term "reduced scattering coefficient" instead of the "transport scattering coefficient". It seems appropriate to recall also several recent publications on various problems of thermal engineering, geophysics, and aerospace engineering (Dombrovsky et al., 2016; Dombrovsky et al., 2017; Dombrovsky et al., 2018; Dombrovsky et al., 2019; Dombrovsky et al., 2020; Krainova et al., 2017; Dombrovsky and Randrianalisoa, 2018), a fairly accurate solution of which was obtained using the transport approximation.

Due to the linearity of the radiative transfer equation, the traditional technique can be used: the radiation intensity at each point of the medium is presented as a sum of the diffuse component and the directional incident radiation, which is exponentially attenuated in the medium (Sobolev, 1975). As a result, it is sufficient to focus on more complex problem for the diffuse radiation.

The second feature of the problem being solved suggests a possibility of a simple description of the angular dependence of the diffuse component of the radiation field. It is known that this approach leads to one of the simplest differential approximations: either to the known P_1-approximation, or to the modified two-flux approximation taking into account the effect of total internal reflection at the body surface (Dombrovsky et al., 2006). In both cases, the calculation of the power field of the radiation absorbed in the medium is reduced to solving a boundary value problem for an ordinary differential equation of the second order. The choice between the named differential approximations is determined by the dimension of the problem and the type of boundary conditions (Dombrovsky et al., 2012, 2015). Comparison with exact numerical calculations for a typical problem of laser hyperthermia (Dombrovsky et al., 2013) showed that the modified two-flux method gives rather accurate results when solving one-dimensional problems. At the same time, the classical diffusion approximation (P_1), which ignores the discontinuity in the angular dependence of the radiation intensity on the irradiated surface, is more universal, since it is applicable for computational regions of complex shapes. As for the relatively large error of P_1 near the body surface, this disadvantage turns out to be insignificant, for example, when cooling the surface, which

is recommended for the promising peripheral heating of the tumor (Dombrovsky et al., 2012).

TRANSIENT HEAT TRANSFER MODEL

The simplest and frequently used description of heat transfer in the human body is based on the so-called bioheat equation proposed in the early work by Pennes (1948). It was assumed that the arterial blood temperature, T_b, is uniform throughout the tissue while the venous blood temperature is equal to the local tissue temperature T_t. The resulting transient energy equation is as follows:

$$(\rho c)_t \frac{\partial T_t}{\partial t} = \nabla(k_t \nabla T_t) + \rho_b c_b \omega_b (T_b - T_t) + W_m \qquad (1)$$

where the second term on the right-hand side is responsible for the heat transfer due to arterial blood perfusion of rate ω_b, and the last term W_m is the metabolic heat generation within the tissue. Approximate **Eq. 1** contains obvious physical contradictions. It is assumed that heat transfer from arterial blood does not depend on the diameter of the blood vessels, whereas in many parts of the body there are only thinner vessels and capillaries. This equation does not take into account the cooling of arterial blood. This can be applicable only to estimate the volumetric heat transfer in internal organs containing large vessels of arterial blood.

A more general model for heat transfer in human tissues should be based on two coupled energy equations for the tissue and arterial blood with the spatial and time variation of the arterial blood temperature (Khaled and Vafai, 2003; Nakayama and Kuwahara, 2008). The models of this type have been considered in early paper by Xuan and Roetzel (1997) and also in more recent publications (Dombrovsky et al., 2012; He and Liu, 2017; Wang et al., 2018; Andreozzi et al., 2019; Dutta and Kundu, 2019).

In this paper, we consider only superficial tumors. This simplifies significantly the calculations of heat transfer. There are several layers of biological tissue at the surface of the body: a thin epidermis that does not contain blood vessels, dermis (sometimes subdivided into several layers) and a fat layer with a small number of capillaries. The fat layer is followed by the muscle layer with more arteries. Superficial tumors, as a rule, are concentrated in the dermis, can penetrate into the fat layer, but do not reach the muscle layer. According to (Dombrovsky et al., 2012), the difference between the temperature of tissue and arterial blood in the fat layer and epidermis is negligible and heat is transferred from the muscle layer to the body surface mainly by conduction.

Obviously, there is no need in a separate energy equation for blood in the human skin, and the heat transfer during hyperthermia can be calculated using the following simple equation:

$$(\rho c)_t \frac{\partial T_t}{\partial t} = \nabla(k_t \nabla T_t) + W_m + W_{rad} \qquad (2)$$
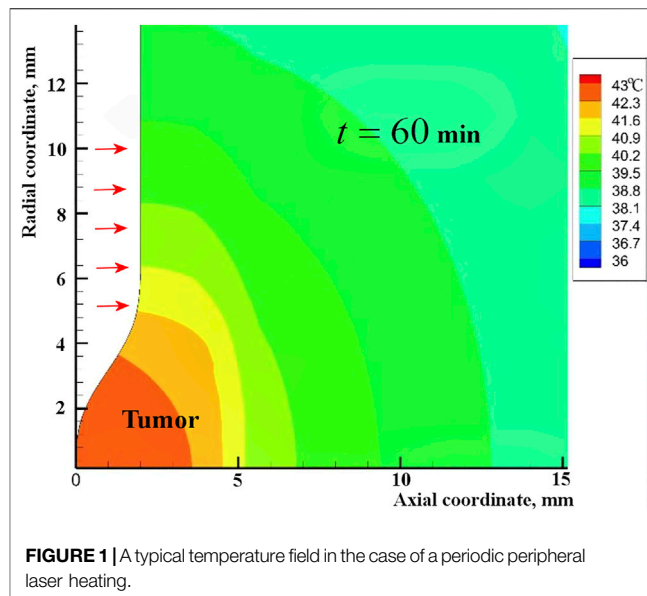
where the last term is the absorbed radiation power.

FIGURE 1 | A typical temperature field in the case of a periodic peripheral laser heating.

Eq. 2 seems too simple to suggest an original tumor heating method. Fortunately, this is not the case, and the author's experience in calculating the transient temperature fields in structures of complex shapes made it possible to suggest an interesting way of uniformly heating the tumor. This is the so-called indirect heating strategy.

It is known that direct laser heating of a superficial tumor can lead to an undesirable protective reaction of the body with an increase in local perfusion. Periodic heating of only the annular region around the tumor using a scanning laser beam proposed by Dombrovsky et al. (2012) radically changes the strategy of hyperthermia. During the long pauses between heating periods, heat is transferred to the tumor by conduction. In this case, the tumor is heated uniformly from several sides (**Figure 1**). The human thermal regulation system is not designed to receive an additional heat from the body volume (not from the body surface), and such heating should not cause a significant increase in perfusion. Heating of healthy tissue around a tumor can be enhanced by introducing gold nanoparticles into the illuminated area, but embedding the nanoparticles into biological tissues is related with serious additional difficulties, instead of which it is sufficient to increase the power of incident laser radiation.

When calculating both the field of the absorbed radiation power and transient axisymmetric temperature field in the tumor and surrounding healthy tissues, it is possible to use the universal finite element method, which is more convenient for computational regions of complex shape (Chen, 2011; Zienkiewicz et al., 2013), as was done in (Dombrovsky et al., 2012).

Sometimes, it is possible to use a simpler and more economical finite-difference method. In the heat conduction part of the problem, the implicit scheme of the second order of approximation with splitting the spatial differential operator into two parts and alternately integrating the equation at each

time step along a set of grid lines in the axial and radial directions is preferable (Dombrovsky et al., 2015).

It is known that when using the finite element method, the problem is reduced to solving a system of algebraic equations with a matrix in which nonzero elements form a rather wide band along the diagonal of the matrix. The width of the band depends on a particular procedure for numbering the nodes of the finite element model. When using a finite-difference algorithm with splitting the problem into alternating heat propagation in orthogonal directions, the width of a similar band of nonzero matrix elements is equal to three. Therefore, the calculations by the program using the finite-difference method turns are much faster. In the numerical solution of transient axisymmetric problems with equally detailed discretization of the computational region and the same time steps, according to the author's experience, the finite-difference solution is about six times faster than when using the finite element method. I am talking about my home codes, which differed only in the numerical solution of the problem.

It is important to note that the use of peripheral heating of the tumor can be accompanied by water cooling of the irradiated body surface, where most of heat receptors are located. One can find some details about the cutaneous temperature receptors and the pain related with the heating the body surface in (Spray, 1986; Lorenz et al., 2002; Kobayashi, 2015). The water cooling the body surface makes the suggested strategy almost painless and allows longer sessions with detailed control of the process parameters.

Heating the normal human tissue around the tumor is relatively low due to significant radial spreading of heat (see **Figure 1**). At the same time, this heating is extremely important because the red blood cells of arterial blood lose a part of the oxygen they carry (Collins et al., 2015). Moreover, a favorable factor is the possible destruction of some overheated capillaries at the border of the tumor due to the release of gases in the heated blood. As a result, the oxygen regeneration of tumor tissue decreases. In fact, the peripheral heating is accompanied by asphyxiation of the tumor with its partial or complete necrosis. The latter is an important part of the recommended heating strategy.

It goes without saying that the suggested method of laser-induced hyperthermia of superficial tumors does not exclude alternative approaches, such as that proposed in the recent study by Yin et al. (2020).

NON-ARRHENIUS KINETICS OF THERMAL DAMAGE

In many publications on the modeling of hyperthermia, the kinetics of thermal degradation of tumor tissue is described by the classical Arrhenius equation, which can be written as follows (Dewey, 2009):

$$\frac{\partial \xi}{\partial t} = (1 - \xi)A \exp\left(-\frac{E}{RT}\right) \quad \xi(0) = 0 \tag{3}$$

where ξ is the degree of thermal destruction, E is the activation energy, and the initial condition means a conventional beginning

of the process. The values of A and E should be determined experimentally.

The Arrhenius's law correctly describes the known physical phenomenon: the exponential intensification of thermal destruction with increasing temperature. Nevertheless, when trying to apply this law to living human tissue, it becomes obvious that the above formulation cannot be immediately employed. It is enough to compare the state of, for example, a piece of meat left in a warm room with air temperature about 37°C (outside the fridge), and the state of the muscle tissue of a living person. In no case can one ignore the continuous process of regeneration of human tissues due to arterial blood flow, which supplies the cells of the body with oxygen. Of course, the last statement is true for tumor tissues.

An attempt to take into account the regeneration of living tissues when describing their possible damage during hyperthermia by modification of **Eq. 3** was undertaken in (Dombrovsky and Timchenko, 2015) (see also (Dombrovsky, 2019)):

$$\frac{\partial \xi_i}{\partial t} = (1 - \xi_i)A_i exp\left(-\frac{E_i}{RT}\right) - B_i\xi_i\omega_b \tag{4}$$

$$\xi_i(0) = 0 \quad i = 1,...,6$$

where $i \leq 5$ are the numbers of skin layers, $i = 6$ corresponds to the tumor tissue, and B_i are the dimensionless coefficients. It was assumed in that $B_i = B_h \gg 1$ for all the healthy tissues, whereas $B_6 = 0$ (for the totally destroyed regeneration of the tumor tissue). The last assumption is supported by experimental data for very high sensitivity of red blood cells to the overheating expected at the periphery of the tumor (Gershfeld and Murayama, 1988; Fasano et al., 2010). It should be noted that when using the traditional **Eq. 3**, which does not take into account the regeneration of living biological tissues, the formal solution gives an incorrect result with noticeable thermal damage to these tissues already within several tens of minutes of thermal therapy. At the same time, the use of the kinetic model (4) gives a qualitatively correct result, indicating damage only to the tumor, which does not receive oxygen-rich arterial blood during the recommended peripheral heating (Dombrovsky, 2019).

Strictly speaking, the loss of oxygen by erythrocytes during heating of arterial blood as it approaches the heated tumor can also be described by the Arrhenius law with some values of the activation energy and the coefficient before the exponent.

The loss of oxygen by erythrocytes of arterial blood heated at the periphery of the tumor can be significant only for superficial tumors, which are approached by relatively thin blood vessels and capillaries. In this case, the average velocity of blood flow is small and the time of its heating is sufficient for a significant decrease in the oxygen content in erythrocytes.

It is important to remind that the present work is not related to tumors far from the surface of the body, in places where there are significantly larger arteries. The relatively rapid flow of blood through the large arteries makes it impossible any thermal degradation of erythrocytes. The discussed strategy of

indirect/peripheral heating of such tumors is also not expected to be applicable.

In addition, with the slow thermal treatment of the tumor, more detailed kinetic models should consider multi-stage conversions in tumor cells (Feng and Fuentes, 2011; Pearce, 2013; Crapse et al., 2021). This means that a complete Arrhenius equation includes several exponential terms responsible for these stages of the process. Such a complete description of the kinetics of thermal damage of tumor tissues is not associated with additional mathematical difficulties. However, there are no reliable data in the literature for the parameters of the detailed kinetic models applicable for various tumors. Therefore, currently, as a rule, simpler models are used and multi-stage kinetic models are beyond the scope of the present paper.

CONCLUSION

A discussion of physical and computational modeling of heat transfer in laser-induced hyperthermia of superficial human tumors is presented, including differential models for radiative transfer, various approaches to the analysis of transient heat transfer, and possible modifications of traditional kinetic models of thermal degradation of tumors.

In radiative transfer modeling, the transport approximation and differential models are recommended for the diffuse component of the radiation field which contributes a lot to the absorbed radiation power. The heat transfer in a multilayer skin can be approximately calculated using the transient energy equation taking into account mainly two modes of heat transfer: the ordinary heat conduction and volumetric heat generation due to the absorbed external radiation. In kinetics of the tumor degradation, it is shown that a partial regeneration of normal human tissues at the periphery of the tumor due to oxygen supplied with the arterial blood should not be ignored.

When modeling radiative transfer, it is recommended to use the transport approximation for the scattering phase function and one of the differential models for the diffuse component of the radiation field, which makes the main contribution to the absorption of laser radiation. Heat transfer in a multilayer

human skin can be calculated using the transient energy equation, which takes into account two main effects: ordinary heat conduction and volumetric heat due to the absorbed radiation power. In the kinetics of tumor damage, it has been shown that one should not ignore the partial self-regeneration of normal tissues at the tumor periphery due to oxygen supplied with arterial blood.

The motivation and advantages of the previously suggested painless procedure of a peripheral/indirect periodic heating of the tumor with a focus on the tumor asphyxiation are clarified in detail. It is expected that this discussion will be instructive for alternative procedures developed by other researchers as well.

The author hopes that this paper will be useful for young and not so experienced researchers to overcome some typical weaknesses of computational modeling the photothermal treatment of superficial tumors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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NOMENCLATURE

A coefficient in the Arrhenius equation, s^{-1}

B coefficient in **Eq. 4**, dimensionless

c specific heat capacity, J/(kg K)

E activation energy, J/mol

k thermal conductivity, W/(m K)

W volumetric power, W/m^3

Greek symbols

ξ degree of tissue degradation, dimensionless

ρ density of tissue, kg/m^3

ω rate of blood perfusion, s^{-1}

Subscripts and superscripts

b Arterial blood

h healthy

m metabolic

rad radiative

t human tissue