Local Thermal Coagulation due to Laser-Tissue Interaction as Irreversible Phase Transition

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Abstract

A new mathematical model is proposed for the growth of a small necrosis domain in living tissue caused by local laser irradiation. Laser light is assumed to be delivered to a small internal region where its absorption causes the temperature to attain high values, leading to immediate tissue coagulation. The coagulation is treated in terms of irreversible phase transition, i.e., it is assumed to occur after the tissue temperature exceeds a certain threshold T_{cg}. The model considers tissue as involving two regions: the necrosis domain, where the blood perfusion rate is equal to zero, and the normal tissue, which responds to temperature variations by increasing the perfusion rate. The model takes into account the fact that in normal tissue changes in temperature are governed by the blood perfusion rate averaged on spatial scales over the length of the vessels directly controlling heat exchange between the tissue and blood rather than the true perfusion rate. Two alternative models, the developed one and a model allied to the classic approach to the mathematical description of local thermal coagulation, are compared. The effects of blood flow nonuniformity and the delay in vessel response on growth of the necrosis domain are analyzed in detail. © 1997 Society of Photo-Optical Instrumentation Engineers.

Keywords thermal coagulation; laser coagulation; necrosis growth; perfusion rate; thermoregulation; thermal modeling.

1 Introduction

Modeling of the necrosis growth caused by thermal coagulation due to, for example, local absorption of laser light, is required for optimizing thermal treatments. However, the mathematical description of bioheat transfer, one of the main elements of this analysis, is far from being well developed[1] because living tissue is a nonlinear (active) medium with a complex structure. The bioheat transfer problem becomes more complicated when a necrosis domain occurs in the tissue. Indeed, in this case the blood perfusion rate $j(\mathbf{r},t)$, as well as the temperature distribution $T(\mathbf{r},t)$, is extremely nonuniform.[2] In addition, it is necessary to consider heat propagation not only into the normal tissue but also through a layer of partly damaged tissue that separates the necrosis domain and the normal tissue.

In the past few decades, a number of models[3–10] for bioheat transfer have been proposed which take into account different features of living tissue. For a review, analysis, and criticism of these models, see, for example, Refs. 1 and 11 through 15. Because of the discrepancy among them, the use of the follow-ing phenomenological bioheat equation generalizing the results obtained has been suggested:[16]

$$c_t \rho_t \frac{\partial T}{\partial t} = \nabla(\kappa_{\text{eff}} \nabla T) - f c_b \rho_b j (T - T_a) + q_h. \quad (1)$$

Here T is the tissue temperature, T_a is the temperature of blood in the large arteries of the systemic circulation, c_t and ρ_t are the density and heat capacity of the tissue, c_b and ρ_b are the same quantities for blood, κ_{eff} is the effective thermal conductivity, q_h is the heat generation rate caused by metabolic processes as well as external power sources, and j is the blood perfusion rate specified as the volume of blood going through a tissue region of unit volume per unit time. The cofactor f, ranging from 0 to 1,[1] is due to heat exchange between arterial and venous blood flowing through the nearest vessels (the countercurrent effect[9]), and the effective thermal conductivity κ_{eff} exceeding the true thermal conductivity κ of the cellular tissue by severalfold[17] accounts for the convective heat transport with blood flow.[7,9] In the equation given, the cofactor f and the ratio $\kappa_{\text{eff}}/\kappa$ are phenomenological parameters.

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In addition, as an inherited feature, the blood perfusion rate j is assumed to be practically uniform on scales of the order ℓ^* characterizing the tissue heterogeneities from the standpoint of heat transfer. The value ℓ^* is about $[\kappa/(c_t \rho_t j)]^{1/2}$ (Ref. 5) and for typical values of the tissue parameters, $\ell^* \sim 1$ cm. We note that the same spatial scales also roughly characterize temperature nonuniformities as follows from Eq. (1). The blood flow considerably affects the temperature distribution in the tissue during laser-induced interstitial thermotherapy.[2,18]

Living tissue is an active medium, i.e., it responds to temperature variations by increasing the blood vessel radius, which gives rise to an increase in the blood perfusion rate j. The blood perfusion rate can grow locally by tenfold;[19] thus, this effect is significant. The live tissue tries to keep its temperature from exceeding a certain vital boundary $T_+ \approx 44$ to $46\,°C (T < T_+)$ to prevent thermal damage (see, e.g., Ref. 20). So the main increase in the blood perfusion rate j should fall between the temperature variations from T_a to a certain value $T_{vr} \approx T_+$; after the temperature exceeds the value T_{vr}, the blood perfusion rate j is likely to depend only weakly on temperature because the blood vessels have exhausted their ability to expand.

In order to analyze temperature distribution, typically the dependence $j(T)$ obtained experimentally is used. However, whether such a dependence holds when the temperature distribution becomes substantially nonuniform is a question. Indeed, in this case due to the extent of the vessels controlling heat exchange between blood and cellular tissue, the dependence $j(T)$ can not only alter its particular form but can also take a functional form when the blood perfusion rate $j(r)$ at a given point $\mathbf{r}$ is determined by the whole temperature distribution $\{T(\mathbf{r}')\}$ over a certain neighborhood of this point (for similar behavior of the tissue response to variations in CO_2 concentration, see, e.g., Ref. 21). The specific details of the mechanism by which living tissue responds to local temperature variations on scales of about 1 cm are also a question.[21] However, under strong heating localized on such scales, thermal autoregulation can be effectively implemented through the response of the microcirculatory bed to reduced O_2 partial pressure or increased concentration of metabolism products (e.g., CO_2, H^+, and adenosine diphosphate (ADP)) because higher temperatures result in intensified metabolism with a higher O_2 consumption. In addition, this explains a possible delay of the tissue response to temperature variations and enables the corresponding delay time to be estimated at several minutes (see, e.g., Ref. 21).

When considering living tissue with a necrosis domain, one should take into account the effect that partial damage has on heat propagation. However, the models[2,22,23] based on expressions similar to

$$j = \zeta j_n(T), \qquad (2)$$

where ζ is the fraction of undamaged tissue and $j_n(T)$ is the blood perfusion rate that would occur in tissue without damage, can be justified at the qualitative level only. So, if one would like to describe heat propagation through partly damaged tissue in detail, then a more sophisticated theory should be developed.

In this paper we propose a model for heat transfer in living tissue containing a necrosis domain that allows for the aforementioned features. The main purpose is to describe this model and to analyze its basic characteristics, comparing it with the models developed previously and allied to the classic approach to the mathematical description of local thermal coagulation (see, e.g., Refs. 2 and 18), rather than to simulate the time course of a real treatment. So we confine ourselves to analysis of thermal coagulation in living tissue without tumors and consider the growth of a ''one-dimensional'' necrosis domain.

2 MODEL BACKGROUND

In order to obtain a more rigorous equation governing evolution of the temperature, we should take into account the fact that living tissue is an active heterogeneous medium organized hierarchically. In other words, to obtain the desired macroscopic bioheat equation from the microscopic equations individually governing heat diffusion in cellular tissue and convective heat transport via blood inside vessels, we have to take into account the following. First, heat propagation in living tissue on scales of about 1 cm is mainly controlled by blood flow through the vascular network in spite of the fact that its relative volume is small[5] (living tissue as a heterogeneous medium). Second, blood vessels make up a highly branching vascular network approximately of a tree form, so distribution of blood flow over the vascular network as well as over the tissue domain is characterized by strong correlations between different levels of hierarchy and also by spatial correlations (living tissue as a hierarchically organized medium). Therefore, when averaging the microscopic equations, we have to regard the vascular network as a whole rather than as a collection of individual vessels independent of each other. Third, the hydrodynamic resistance of vessels to blood flow can depend on time due to the tissues reaction to temperature variations (living tissue as an active medium).

In Ref. 24 we developed an averaging technique that has enabled us to reduce the microscopic governing equations to a system of macroscopic equations that regard living tissue as a continuous medium with certain properties. In particular, we have shown in Ref. 24 (see also Refs. 25 through 27), where we reproduced some results obtained first by Chen and Holmes,[5] that the macroscopic bioheat equation actually deals with the tissue temperature $T(\mathbf{r},t)$ averaged on spatial scales about the mean

length l_v of the vessels directly controlling heat exchange between cellular tissue and blood. The equation obtained for the tissue temperature practically coincides with the bioheat equation (1) with the replacement of the true perfusion rate $j(\mathbf{r})$ by one $j_v(\mathbf{r})$ averaged on scales l_v. The characteristic length l_v of averaging in turn depends on the local value $j_v(\mathbf{r})$ of the averaged perfusion rate, namely, $l_v \sim [\kappa/(c_t \rho_t j_v)]^{1/2}$. Therefore, the relationship between the averaged blood perfusion rate $j_v(\mathbf{r})$ and the true one $j(\mathbf{r})$ is specified by a certain nonlinear equation, which can be approximately represented in the following form[24]:

$$j_v - \nabla(l_v^2 \nabla j_v) = j. \qquad (3)$$

In addition, it has been found that the constants f and F are specified by the vascular network architectonics only, in particular, $F \sim 1/f \sim [\ln(l/a)]^{1/2}$, where l/a is the mean ratio of length to radius of individual blood vessels. For real microcirculatory beds, a typical value of the ratio l/a is about 40,[21] which enables us to estimate these constants as $F \sim 2$ and $f \sim 0.5$.

In order to describe local thermoregulation, we need to specify how each vessel responds to the corresponding piece of information characterizing the state of the tissue, in particular its temperature. So, in deriving the equation relating the blood perfusion rate $j(\mathbf{r},t)$ to the tissue temperature $T(\mathbf{r},t)$, we make use of the following physiological data.[21] Local autoregulation of blood perfusion in living tissue on scales of about 1 cm is due to expansion or contraction of the blood vessels making up a single microcirculatory bed, and blood redistribution over this vascular network is mainly controlled by a large group of arteries that differ in length significantly. The reaction of the microcirculatory bed is governed by receptors responding to variations in CO_2 partial pressure, H^+ concentration, or other metabolism products. However, as mentioned in Sec. 1, under strong heating such receptors can play the role of effective thermosensors, supplying the microcirculatory bed with essential information. Obviously, none of the vessels receives complete information on the tissue state, so there must be a certain cooperative mechanism for information self-processing by which the behavior of different vessels is kept consistent with each other so that the tissue can respond properly.

We have shown[24,26] that such a cooperative mechanism of self-regulation can be implemented through the vessels response to the blood temperature in the corresponding veins. The receptors mentioned above are located directly in the cellular tissue as well as embedded in the walls of vessels, including veins.[21] Those embedded in the vessel walls are able to measure the concentration of the metabolism products directly in blood and thus to effectively measure its temperature. For small vessels (arteries and veins), the position of the receptors governing their behavior is not a factor. This allows us to make use of the proposed cooperative mechanism of self-regulation in the description of tissue response to local and strong heating.

Under the adopted assumptions it turns out[24,26] that for normal tissue, the dependence of blood perfusion rate j on temperature T can be approximately described by a local equation relating the values $j(\mathbf{r})$, $T(\mathbf{r})$ taken at the same point $\mathbf{r}$ until the temperature approaches to the vital boundary T_+. This is due to the cooperative mechanism of self-regulation which involves the response of each vessel to the corresponding piece of information and the coordination of the behavior of all the vessels by the self-processing of information. The adequate self-processing of information is implemented through heat conservation as blood mass inside the relatively large veins of the microcirculatory bed.[26] The vascular network whose behavior is governed by this mechanism can supply each region of the cellular tissue with blood at a rate that meets its individual demand, and different regions of the cellular tissue do not interfere with one another. The equation obtained for the tissue response is of the form

$$\tau \frac{\partial j}{\partial t} + j \frac{T_+ - T}{T_+ - T_a} = j_0, \qquad (4)$$

where τ is the delay time of the tissue response and j_0 is the blood perfusion rate, provided the tissue is not affected. This result also holds true for living tissue containing a small necrosis domain[24,28] because the temperature of blood in veins whose length exceeds their size by severalfold is not sensitive to the presence of a necrosis domain.

Mathematical description of heat transfer in partly damaged tissue is a more complicated problem. For example, partial damage of the vascular network embedded into such tissue can give rise to domains with extremely low blood perfusion that have a fractal geometry.[29] However, in a mathematical description of thermal coagulation, the particular regularities of heat propagation in partly damaged tissue are of little importance. In fact, during thermal treatment based on thermal coagulation, high temperatures on the order of 100 °C are attained and the typical time of the treatment is several minutes. At such temperatures, the characteristic time t_{thr} of thermal coagulation depends heavily on the temperature; in particular, for $T=65$, 70, and 75 °C, the values of t_{thr} are 100, 20, and 5 s, respectively.[30] The mean time during which the necrosis domain can grow substantially is about 2 min (for $j_0 \sim 0.01$ s^{-1}) and the temperature drops from a value of about 100 °C at its center to the normal temperature (≈ 37 °C) at distant points. Therefore, under such conditions, the region in which the thermal coagulation is under way is a thin layer compared to the necrosis domain. This layer separates the necrosis from the normal tissue and is char-

acterized by a narrow temperature interval ($T_{cg}-\Delta$, $T_{cg}+\Delta$), where $T_{cg} \approx 60$ to 70 °C and $\Delta \sim 5$ °C. The latter enables us to ignore the thickness of this layer, i.e., to treat it as the boundary of the necrosis domain and to ascribe to it the fixed temperature T_{cg}.

In other words, within the framework of such an approach, thermal coagulation is considered in terms of an irreversible phase transition. Moreover, owing to the discreteness of the vessel arrangement, the temperature distribution in living tissue exhibits random nonuniformities that are not described by Eq. (1). The amplitude of these nonuniformities turns out to be also on the order of 5 °C for such a high overheating of the tissue.[24] The presence of large vessels can increase the amplitude of temperature nonuniformities.[8,31] Thus it seems to be meaningless to analyze in detail the properties of the partial damage layer based on mean field equations similar to (1). Keeping in mind the aforesaid, we propose the following model.

3 FREE BOUNDARY MODEL

We assume that laser light is delivered to an internal region of living tissue where, owing to its absorption, the temperature attains high values (above 60 to 70 °C), leading to immediate thermal coagulation of the tissue, including coagulation of blood in the vessels passing through this region. It should be pointed out that in the given model, the laser light plays solely the role of a source of heat, so this model also holds for local coagulation caused by other mechanisms of superficial heating, for example, electrocoagulation. Heat diffusion into the surrounding tissue causes its further coagulation, giving rise to growth of the necrosis domain. Thermal coagulation is treated in terms of the irreversible phase transition that occurs after the temperature exceeds a certain threshold $T_{cg} \sim 60$ to 70 °C. Inside the necrosis domain, heat diffusion is controlled only by thermal conduction of the cellular tissue. Heat propagation into the surrounding tissue is governed by both thermal conduction and blood flow, with the latter causing the renormalization of thermal conductivity, $\kappa \rightarrow \kappa_{eff}$, as well as giving rise to an effective heat sink. If a large artery or vein is located in the immediate vicinity of the necrosis region, then blood flow in this single vessel can affect heat transfer substantially and the bioheat equation should be modified.[8,31] The case described, however, deserves an individual investigation.

The tissue with necrosis is considered as involving two regions: the necrosis domain Q_{cg} where the blood perfusion rate is equal to zero,

$$j(\mathbf{r},t)=0 \quad \text{for } \mathbf{r} \in Q_{cg}, \qquad (5)$$

and the normal tissue Q_n that responds to temperature variations by locally increasing the blood perfusion rate $j(\mathbf{r},t)$. In addition, we allow for the fact that the tissue response can be delayed. Blood ves-

sels can expand to only a certain extent as the temperature increases. When it becomes high enough, $T > T_{vr}$, the blood perfusion rate $j(\mathbf{r},t)$ attains a large but finite value j_{max} and remains approximately constant. Taking into account expression (4), we describe this behavior of normal tissue by the equation

$$\tau \frac{\partial j}{\partial t}+j\Phi(T)=j_0 \quad \text{for } \mathbf{r} \in Q_r. \qquad (6)$$

Here τ is the delay time of the tissue response and the function $\Phi(T)$ is of the form

$$\Phi(T)=\begin{cases} \epsilon+(1-\epsilon)\dfrac{T_{vr}-T}{T_{vr}-T_\alpha} & \text{for } T<T_{vr} \\ \epsilon & \text{for } T>T_{vr} \end{cases}, \qquad (7)$$

where the ratio $\epsilon=j_0/j_{max}$ is a small parameter, $\epsilon<1$.

In the necrosis domain Q_{cg}, the tissue temperature obeys the heat diffusion equation for solids:

$$c_t\rho_t \frac{\partial T}{\partial t}=\kappa\nabla^2 T+q_h, \qquad (8)$$

where κ is the intrinsic tissue conductivity and q_h is the rate of heat generation due to laser light absorption. Inside the normal tissue the temperature is governed by the equation

$$c_t\rho_t \frac{\partial T}{\partial t}=F\kappa\nabla^2 T-fc_b\rho_b j_v(T-T_\alpha)+q_h. \qquad (9)$$

Here j_v is the blood flow rate averaged on spatial scales on the order of $[\kappa/(c_t\rho_t j_v)]^{1/2}$ and the constants $F>1$ and $f<1$ are the order of unity. At the interface Γ between the necrosis domain and normal tissue, the temperature and the heat flux are assumed to have no sharp changes, i.e., the temperature distribution meets the following boundary conditions:

$$T|_{\Gamma+0}=T|_{\Gamma-0}, \quad F\nabla_n T|_{\Gamma+0}=\nabla_n T|_{\Gamma-0}. \qquad (10)$$

Inside the normal tissue, the temperature cannot exceed the coagulation temperature T_{cg}, i.e.,

$$T(\mathbf{r},t)<T_{cg} \quad \text{for } \mathbf{r} \in Q_n, \qquad (11)$$

and at the interface Γ, the boundary value T_i is either equal to the coagulation temperature, $T_i=T_{cg}$, or rigorously less: $T_i<T_{cg}$. The former case takes place when the temperature near the interface Γ closely approaches the value T_{cg} and the interface has to move in order to keep up the boundary temperature T_i inside the interval $T_i \lesssim T_{cg}$. In the second case the interface is fixed. Both these conditions can be formally described by the expression

$$(T_i-T_{cg})\left(\frac{\partial T}{\partial t}\bigg|_\Gamma-\frac{\partial T_i}{\partial t}\right)=0, \qquad (12)$$

where the boundary temperature $T_i(\mathbf{s},t)$ is treated as a function of the interface coordinates $\mathbf{s}$ and the time t. For points distant from the necrosis domain,

$$T|_\infty = T_a. \tag{13}$$

Finding the relationship between the averaged and true blood flow rates, $j_v(\mathbf{r},t)$ and $j(\mathbf{r},t)$, we have taken into account the fact that the scale l_v of averaging, in its turn, depends on the local value of $j_v(\mathbf{r},t)$. The latter and expression (3) enable us to write

$$j_v - \frac{\lambda\kappa}{c_t\rho_t}\nabla^2 \ln j_v = j, \tag{14}$$

where λ is also a constant on the order of unity.

Equation (14) should be subjected to a certain boundary condition at the interface Γ because it makes no sense to average the blood perfusion rate over the necrosis domain impermeable to blood. The physical layer separating the necrosis domain and the normal tissue where the local vascular network is not damaged is complex in structure and contains a spatial increase of the blood perfusion rate from zero to the value in the normal tissue. In order to avoid the problem of analyzing the blood perfusion rate in this layer, we take into account the following simplifying circumstance. On one hand, the typical size of the necrosis domain formed during a thermal therapy course and the characteristic length of temperature variations are of the same order, about 1 cm.[2,11] Thus, particular details of spatial variations in the blood perfusion rate on scales much less than 1 cm are not a factor. On the other hand, the damaged part of the vascular network located inside the necrosis domain is most probably made up of an artery and vein that previously supplied this region with blood as a whole, and shorter vessels formed by their branching. Indeed, the mean volume of living tissue supplied by a single small artery (or vein) of a fixed length l is about l^3.[21,29] Thus, the regions where total blood perfusion is directly controlled by different vessels of fixed length do not overlap substantially and the architectonics of the microcirculatory bed can be approximately represented as a binary tree embedded uniformly in the cellular tissue.[29] Therefore, the region containing the part of the vascular network in which blood flow is significantly disturbed because of the necrosis formation does not substantially exceed the necrosis domain. The latter allows us to identify the given layer with the interface Γ, and to deal with a sharp increase in the blood perfusion rate at the necrosis interface. The desired boundary condition imposed on the averaged blood perfusion rate j_v must obey the law of blood conservation, which in this case can be written as

$$\int_{Q_n} d\mathbf{r} j_v(\mathbf{r},t) = \int_{Q_n} d\mathbf{r} j(\mathbf{r},t). \tag{15}$$

So in order to fulfill identity (15) we have to set the normal gradient of the averaged blood perfusion rate equal to zero at the interface Γ

$$\nabla_n j_v|_{\Gamma^+} = 0. \tag{16}$$

We note that this assumption will not hold if a large vessel passes through the necrosis domain. However, the probability of this event is small and this case should be analyzed individually.

The system of expressions (5) through (16) makes up the proposed model. The purpose of this paper is to consider the characteristic features of the proposed model, to compare it with the models[2,18] used previously, and to analyze in detail typical properties of local thermal coagulation described by the given model. This allows us to confine ourselves to the simplest situation which, nevertheless, characterizes a real process reasonably enough.

3.1 ONE-DIMENSIONAL PHANTOM

Let us consider a one-dimensional tissue phantom in which the necrosis domain begins to grow at the point $x=0$. For the sake of simplicity, the depth of laser light penetration into the tissue is assumed to be small. Under these conditions, heat generation can be effectively described in terms of the temperature $T_b=T(0)$ fixed at the point $x=0$ and we may confine our analysis to the half-space $\{x \geq 0\}$. Let us, for example, set the value T_b equal to 100 °C, which reflects the possible control over the temperature by water vaporization when the heat generation rate becomes high enough. In addition, for the sake of simplicity, we ignore the difference between the density and heat capacity of the cellular tissue and blood, setting $c_t=c_b=c$ and $\rho_t=\rho_b=\rho$.

In order to compare the given free boundary model with the models developed previously, we also consider the growth of the necrosis phantom described by the following system of equations that reflects the essence of such models. In the region $x>0$, the temperature distribution $T(x,t)$ and the fraction $\zeta(x,t)$ of undamaged (live) tissue obey the equations

$$c\rho\frac{\partial T}{\partial t} = \kappa\frac{\partial}{\partial x}\left[\tilde{F}(\zeta)\frac{\partial T}{\partial x}\right] - \zeta f c\rho j(T-T_a), \tag{17}$$

and

$$\frac{\partial \zeta}{\partial t} = -\zeta\omega(T), \tag{18}$$

where $\omega(T)$ is the rate of tissue damage due to thermal injury and the function $\tilde{F}(\zeta) = \zeta(\tilde{F}-1)+1$. Taking into account the experimental data[30] for thermal injury, we specify the dependence $\omega(T)$ (where T is in degrees Celsius) by the expression
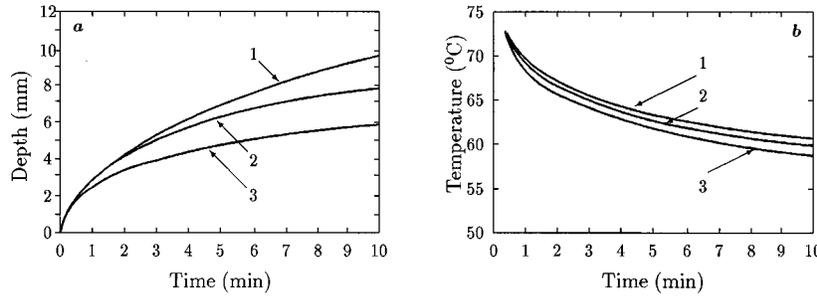
Fig. 1 The size $\Re = x_{0.5}$ of the necrosis domain (a) and the temperature $T_{0.5}$ at its effective boundary (b) versus time for different values of the parameters $\{\epsilon = 1, \text{(curve 1)}\}$; $\{\epsilon = 0.2, \tau = 2 \text{ min, (curve 2)}\}$; $\{\epsilon = 0.2, \tau = 0, \text{(curve 3)}\}$; $(\lambda = 2)$.

$$\omega(T) = 0.2 \times \exp\left[\frac{T - 60}{3.6}\right] (1/\text{min}), \qquad (19)$$

which corresponds to the following temperature dependence of the threshold exposure time t_{thr} (in seconds): $t_{\text{thr}} = 100 \exp\{(64 - T)/3.6\}$. It should be noted that expression (19) is an approximation of the Arrhenius dependence $\omega(T) \propto \exp[-(\Delta H / RT)]$ chosen for the sake of convenience. For the blood perfusion rate j, the governing equation is assumed to be of the same form as Eq. (6).

In the next section we compare the two models using the following typical values of the physical parameters: $T_a = 37\,^\circ\text{C}$, $T_{\text{vr}} = 45\,^\circ\text{C}$ (see Ref. 6), $\kappa \sim 7 \times 10^{-3}$ W/cm×K, $c \sim 3.5$ J/g×K, $\rho \sim 1$ g/cm³, and $j_0 \sim 0.3$ min⁻¹. In addition, we also set the constants $F = 2$ and $f = 0.5$.

4 THERMAL COAGULATION AS AN IRREVERSIBLE PHASE TRANSITION

In order to analyze the growth of a necrosis domain in the framework of Eqs. (6), (17), and (18), we solved them numerically and kept track of the points $x_{0.2}$, $x_{0.5}$, and $x_{0.8}$ specified by the equalities $\zeta = 0.2$, 0.5, and 0.8, respectively. In this way the dynamics of the necrosis growth is characterized by the time dependence of the coordinates $x_{0.2}$, $x_{0.5}$, and $x_{0.8}$ (in millimeters) and the corresponding temperatures (in degrees Celsius) $T_{0.2}$, $T_{0.5}$, and $T_{0.8}$. Different conditions representing various possible limiting cases have been considered. Namely, tissue phantoms without a response to temperature variations, with immediate, and with a delayed response were analyzed. In the first case the blood perfusion rate remains unchanged, $j = j_v = j_0$. For tissue with an immediate response ($\tau = 0$), the perfusion rate can attain large values directly at the beginning of the necrosis growth, whereas for tissue with a delayed response ($\tau > 0$), this increase will occur only after a lapse of time on the order of τ. It could be expected that in all three cases the characteristics of the necrosis growth would be different. Nevertheless, as seen in Figure 1, this statement is justified only with regard to the time dependence of the necrosis size $\Re(t) \equiv x_{0.5}(t)$. (Here necrosis is treated as a region

where $\zeta < 0.5$.) It turns out that the time dependence $T_{0.5}(t)$ of the temperature at the necrosis boundary (interface) Γ is practically the same for all these different cases. Therefore, at least for the tissue under consideration, the necrosis interface can be effectively endowed with certain specific properties, which allows us to treat thermal coagulation in terms of an irreversible phase transition. The latter means that the temperature at the necrosis interface meets certain conditions specifying its value and thereby controls temperature distribution in the tissue. Time variations in the temperature distribution in turn control the motion of the necrosis interface.

In mathematical terms such behavior of necrosis growth is described by the free boundary problem which relates, in general, the temperature T_i at the necrosis interface to its normal velocity ϑ_n and may be the boundary value of the temperature gradient, $\nabla_n T|_i$

$$T_i = T_i(\vartheta_n, \nabla_n T|_i). \qquad (20)$$

However, for necrosis growth due to thermal coagulation, this relationship must be of the logarithmic form because of the exponential dependence of the coagulation rate $\omega(T)$ on the temperature. So, remarkable variations in the dynamics of the necrosis growth can lead to a small alteration of the interface temperature, which is demonstrated in Figure 1. In this paper we deal with the simplest version of such a free boundary model for local thermal coagulation. It is characterized by the assumption that the temperature at the necrosis boundary remains constant. A more sophisticated free boundary model will be developed elsewhere. The given approximation of expression (20), $T_i = T_{\text{cg}}$ (where T_{cg} is fixed), in spite of some roughness, enables us to single out the main characteristics of local thermal coagulation. This is because the spatial distribution of the tissue temperature and, thus the necrosis growth, is not sensitive to small variations in the interface temperature T_i.

Particular details of the necrosis growth from this standpoint are illustrated in Figure 2, which shows
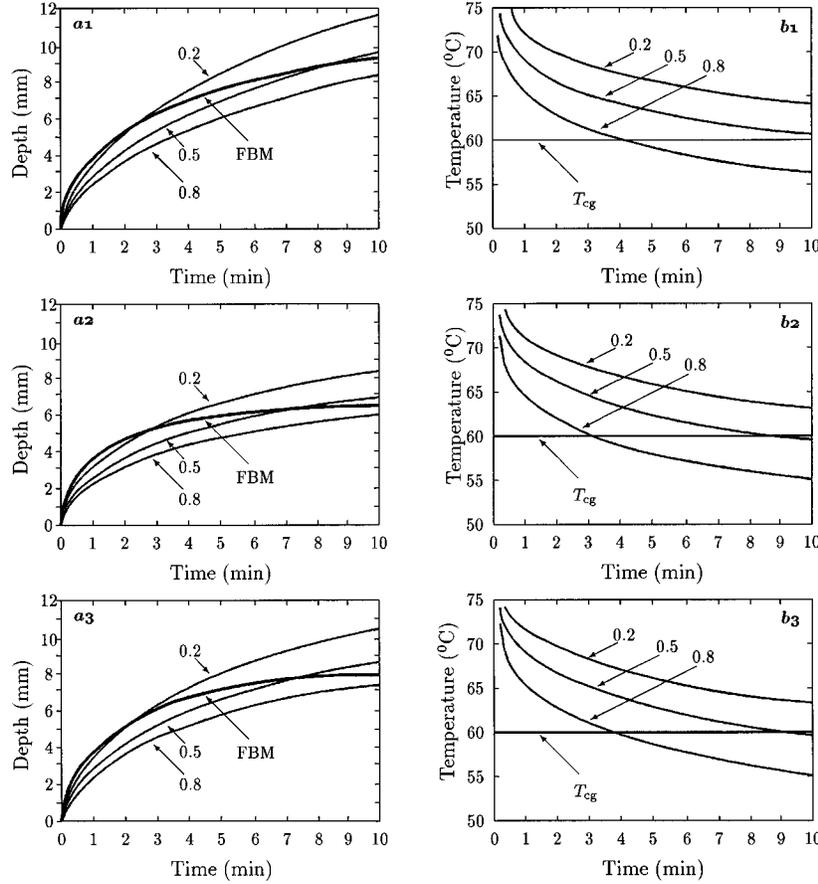
Fig. 2 The time dependence of the coordinates $x_{0.2}$, $x_{0.5}$, and $x_{0.8}$ of the points at which the undamaged tissue fraction ζ=0.2, 0.5, and 0.8 (a1 through a3) and the time dependence of the corresponding temperatures $T_{0.2}$, $T_{0.5}$, and $T_{0.8}$ (b1 through b3) are functions of time for different values of the parameters ϵ, τ. In a1 through a3 the thick lines labeled FBM are the position $\mathfrak{R}$ of the necrosis domain interface in the free boundary model with the temperature coagulation T_{cg} shown in b1 to b3. For a1 and b1, {ϵ=1}; for a2 and b2, {ϵ=0.3, τ=0}; for a3 and b3, {ϵ=0.3, τ=3 min}; (λ=2).

the time dependence of the quantities $x_{0.2}$, $x_{0.5}$, and $x_{0.8}$, and $T_{0.2}$, $T_{0.5}$, and $T_{0.8}$ for a tissue phantom without thermoregulation (j_{max}/j_0=1), one with an immediate strong response to temperature variations (j_{max}/j_0=5, τ=0), and for tissue where a delay in the temperature response has a pronounced effect on thermal coagulation (τ=2 min for the given values of physical parameters, see the next section).

As seen in Figures 2(b1) through 2(b3), the decrease of the temperature $T_{0.5}$ slows sufficiently quickly (within approximately 1 to 2 min) and the temperature $T_{0.5}$ remains inside the interval 60 to 70 °C for about 5 to 10 min, which is a typical duration t_{tr} of thermal treatment based on thermal coagulation. The width of this interval is a sixth smaller than the typical value of the tissue overheating, $T_b - T_a \sim 60$ °C. So to a first approximation, the temperature $T_{0.5}$ may be treated as a fixed constant T_{cg}. Such behavior is actually an additional justification of the proposed free boundary model. In addition, from this it follows that the coagulation temperature T_{cg}, being a phenomenological param-

eter of this model, can be estimated from the expression

$$t_{thr}(T_{cg}) = \frac{1}{\omega(T_{cg})} \sim t_{tr}. \qquad (21)$$

Indeed, under such conditions thermal coagulation proceeds at the temperature T_{cg} and the value of $1/\omega(T_{cg})$ is approximately the time it takes for the live tissue located in the necrosis region to be damaged.[30] Because of the strong temperature dependence of $\omega(T)$, this estimate gives us the value of T_{cg} to sufficient accuracy. In addition, to make the comparison of the two models clearer, we have used in the simulation the value T_{cg}=60 °C found from expression (21) (for $t_{tr}\sim 5$ min) rather than the value of T_{cg} approximating the dependence $T_{0.5}(t)$ to the best degree.

Another characteristic of thermal coagulation is illustrated in Figures 2(a1) through 2(a3). Comparing the time dependence $x_{0.5}(t)$ with the curves "FBM" [describing the motion $\mathfrak{R}(t)$ of the necrosis

interface in the proposed model], we see that there are two stages of necrosis growth. The former corresponds to the time interval $(0, t_{cg})$, where $t_{cg} \sim 1/j_{max} \sim 4$ min. At this stage the necrosis domain grows quickly and in the free boundary model the interface Γ reaches its limit position $\mathfrak{R}_{lim}$. This saturation of the interface displacement is due to the temperature distribution becoming stationary. At the latter stage (from t_{cg} to t_{tr}), the necrosis domain grows slowly and in the free boundary model it is fixed. In other words, the proposed model makes the difference in these stages more pronounced. If the treatment is continued, the real necrosis domain will grow further and after a lapse of 20 to 30 min the necrosis domain will deviate significantly in form from that predicted by the given model. However, such a prolonged treatment is typically used to produce a hyperthermia effect (without visible injury) rather than to cause thermal coagulation directly.[30] Nevertheless, in this case the free boundary model can also be applied after having been modified.

It should be noted that the existence of the two stages does not obviously result from the dependence $T_{0.5}(t)$ because in the model based on Eqs. (17) and (18), the necrosis continues to grow slowly at the second stage too. However, as follows from the model developed, these stages differ from one another not only in the necrosis growth rate but also in the behavior of the temperature distribution. The slow stage is characterized by a quasi-stationary temperature distribution. In other words, at this stage, time scales on which the size $\mathfrak{R}$ of the necrosis domain increases substantially are much larger than time scales on which the temperature distribution becomes steady state, provided the necrosis boundary is fixed. This property is caused by the exponential dependence of the damaged tissue rate $\omega(T)$ on the temperature. At the fast stage, these scales are of the same order.

Concluding this section, we note that the developed model predicts the dynamics of thermal coagulation to the same accuracy as does any model directly dealing with evolution of the field ζ. In fact, as discussed in Secs. 1 and 2, any theory based on equations similar to (17) and (18) cannot reliably describe in detail a layer with partial damage. The motion of this layer is represented in Figures 2(a1) through 2(a3) by the region bounded by the curves $x_{0.2}(t)$ and $x_{0.8}(t)$. So the two models may be treated as practically equivalent if the difference $|x_{0.5}(t) - \mathfrak{R}(t)|$ does not greatly exceed the value $|x_{0.8}(t) - x_{0.2}(t)|$. As seen in Figures 2(a1) through 2(a3), this is the case except for the beginning of the growth and times longer than 10 min.

Moreover, this result actually warrants the feasibility of applying the system of Eqs. (17) and (18) to an analysis of local thermal coagulation. Indeed, one may describe the temperature distribution inside the layer of partially damaged tissue with an equation similar to (17) only if the necrosis growth

does not depend substantially on particular properties of heat propagation through this region. It is this fact which is demonstrated in Figure 2. Under such conditions, either of the two models can be applied; however, it would be more consistent to use a free boundary model that ignores the thickness of this layer, i.e., treats it as the boundary of the necrosis domain. The development of a more sophisticated free boundary model that also allows for time variations of the interface temperature T_i will be the subject of later papers.

5 EFFECT OF TEMPERATURE REGULATION

In this section, based on our model, we study the characteristic properties of thermal coagulation caused by the tissue response to temperature variations. First we consider a tissue with an immediate response, corresponding to $\tau=0$ in Eq. (6). In this case the limit radius $\mathfrak{R}_{lim}$ of the necrosis domain attained during the coagulation is determined by the stationary temperature distribution. In particular, for the tissue phantom without thermal regulation ($\epsilon=1$), the blood perfusion rate is constant, $j=j_0$, and as follows from Eqs. (8) and (9)

$$\mathfrak{R}_{lim}^{\epsilon=1} = \left[\frac{F\kappa}{c\rho f j_0} \right]^{1/2} \frac{T_b - T_{cg}}{F(T_{cg} - T_a)} \sim 1 \text{ cm.} \quad (22)$$

For a tissue with thermal regulation, expression (22), after the replacement $j_0 \rightarrow j_{max}$, may be also used to estimate the value $\mathfrak{R}_{lim}$, thus

$$\mathfrak{R}_{lim} \sim \left[\frac{F\kappa}{c_t \rho_t f j_{max}} \right]^{1/2}. \quad (23)$$

The dynamics of coagulation under such conditions is represented in Figure 3 for different values of the parameter $\epsilon = j_0/j_{max}$.

Figure 3(a) shows the size $\mathfrak{R}$ of the necrosis domain as a function of time. The higher the tissue response, the smaller the necrosis domain and the shorter the fast stage of necrosis growth. The duration of the latter stage is actually the characteristic time t_{cg} during which the size of the necrosis domain attains values about $\mathfrak{R}_{lim}$. Comparing the numerical values of the corresponding quantities, we find that the duration of the fast stage can be estimated by the expression

$$t_{cg} \sim \frac{1}{f j_{max}}, \quad (24)$$

which conforms to the general properties of heat transfer in living tissue. Indeed, in the given model, as follows from Eqs. (8) and (9), the time it takes for the temperature distribution to become a steady-state one is about $f j_{max}$ and the establishment of this steady-state (in reality, quasi-stationary) temperature distribution is actually the essence of the fast stage.
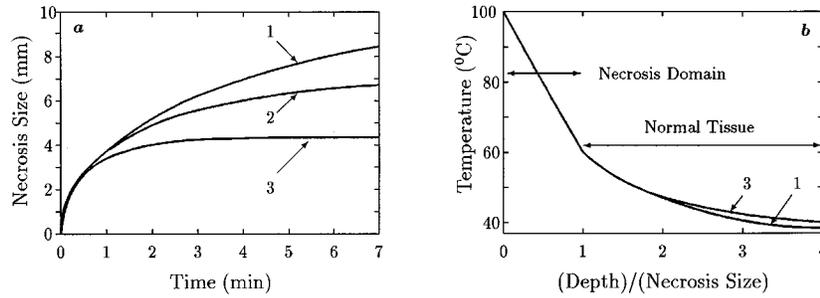
Fig. 3 The size $\mathfrak{R}$ of the necrosis domain versus time (a) and the temperature distribution (b) for different values of ϵ. Curves 1, 2, and 3 correspond to ϵ=1, 0.3, and 0.1, respectively. (τ=0, λ=2).

Figure 3(b) shows the temperature distribution for a tissue without thermoregulation (curve 1) and for a tissue with a strong immediate response (curve 2, j_{max}/j_0=10). In order to compare them with each other, lengths are measured in units of the corresponding necrosis size. It follows from this that, in contrast to the time dependence $\mathfrak{R}(t)$, the tissue response to heating does not affect the form of temperature distribution. This result is in agreement with the conclusion made in the previous section regarding the properties of the temperature at the necrosis boundary.

When the tissue responds to temperature variations intensively enough ($\epsilon \ll 1$), the blood perfusion rate $j(x)$ becomes substantially nonuniform. In this case the averaged perfusion rate $j_v(x)$ differs significantly from the true one $j(x)$, which has a definite effect on the growth of a small necrosis. The latter is illustrated in Figure 4.

Figure 4(a) compares the dynamics of the necrosis growth described by the given model and by the same model where, however, Eq. (14) is omitted and the replacement $j_v \rightarrow j$ is made. Figure 4(b) shows the distribution of the tissue temperature $T(x)$, the true blood perfusion rate $j(x)$, and the averaged one $j_v(x)$ that occur when the tissue responds in such an intensive way. In this case, as seen in Figure 4(b), the averaged blood perfusion rate can be twice as slow as the true one. The latter

has a definite effect on the necrosis growth because ignoring the difference between j_v and j gives a lower estimate of the necrosis size [Figure 4(a)].

Now we consider how the delay in the tissue response can affect thermal coagulation. This effect is remarkable when the delay time τ is comparable with the duration of the fast stage t_{cg}. So we may confine ourselves to values $\tau \sim t_{cg}$.

The difference in dynamics of the growth of the necrosis domain for tissues responding immediately (τ=0) and with a certain delay ($\tau \sim 2$ min) is illustrated in Figures 5 and 6.

As seen in Figure 5(a), when the tissue response is delayed, the necrosis domain initially, grows quickly, keeping ahead of a necrosis domain growing in the tissue with the immediate response. Then the growth of the necrosis domain is suppressed and its form thereafter remains unchanged. It should be noted that in this case the saturation of the necrosis domain growth is not due to the temperature distribution becoming stationary but to an increase in the blood perfusion rate after a time lapse of about τ. Under such conditions there is enough time for the size $\mathfrak{R}$ of the necrosis domain to attain values of on the order of $\mathfrak{R}_{lim}^{\epsilon=1} \propto [1/j_0]^{1/2}$ until the blood perfusion rate increases substantially. These values could not be attained if the tissue response were not delayed. So after the blood perfusion rate increases, subsequent growth of the
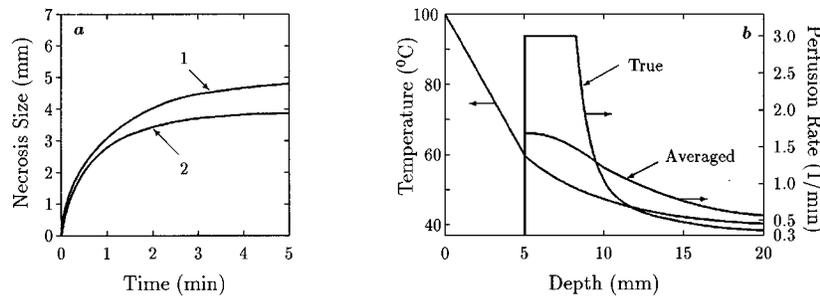
Fig. 4 (a) The size $\mathfrak{R}$ of the necrosis domain as a function of time described by the stated free boundary model (curve 1) and by the same model within the replacement $j_v \rightarrow j$ (curve 2). (b) The distribution of the temperature T, the true perfusion rate j, and the averaged one j_v corresponding to curve 1 at time t=2 min. (ϵ=0.1, τ=0, λ=2, T_{vr}=50 °C).
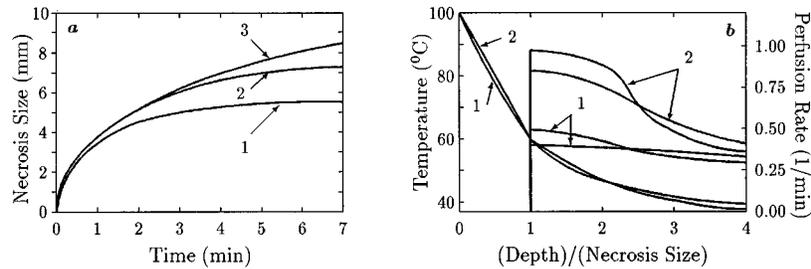
Fig. 5 (a) The size $\Re$ of the necrosis domain versus time for a tissue responding immediately (curve 1) and with a certain delay (curve 2, $\tau=2$ min). Curve 3 represents the $\Re(t)$ dependence for a tissue without thermal regulation. (b) The distribution of the temperature, true and averaged perfusion rates at different time moments $t=1$ min (curve 1) and $t=3$ min (curve 2) for the tissue with delayed response ($\epsilon=0.2$, $\lambda=1$, $\tau=2$ min).

necrosis domain becomes impossible, the temperature T_i at the interface Γ must fall below T_{cg}, and the necrosis domain has to cease to grow. This behavior of the interface temperature is illustrated in Figure 6. It should be noted that such a saturation of the necrosis growth for real tissues seems to be more pronounced because a real necrosis continues to grow at the slow stage until the blood perfusion rate becomes high enough.

Figure 5(b) shows the distribution of the temperature and blood perfusion rate at different moments for a tissue with a delayed response. As before, the length is measured in the corresponding values of the necrosis size in order to compare these distributions. As time elapses, the perfusion rate increases due to the tissue response. In contrast to this behavior of the perfusion rate, the form of the temperature distribution remains unchanged. The comparison of this result with that obtained for the tissue immediately responding to temperature variations [Figure 3(b)], and the results of the previous section, leads us to the conclusion that the form of the temperature distribution occurring in tissue during necrosis growth depends weakly on the particular values of the physical parameters. This conclusion, in particular, forms the basis for applying promising variational techniques to an analysis of thermal coagulation caused by laser–tissue interaction.
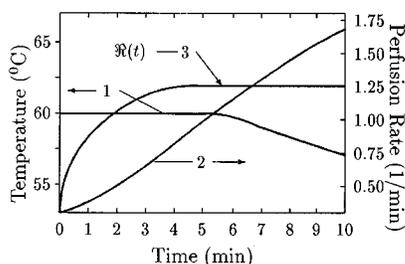
It should be noted that the conclusion concerning the universal form of the temperature distribution has been made by analyzing necrosis growth in tissue phantoms that differ only in the properties of thermoregulation. The other physical parameters (for example, tissue thermal conductivity κ and the initial value j_0 of the blood perfusion rate) take on particular values in the present analysis. This raises the question of whether the stated conclusion will hold if we change these parameters also. However, by choosing the appropriate units of time and length for aggregating such parameters, we can re-write the governing equations in the dimensionless form. Thus their particular values are not the important factor.

6 CLOSING REMARKS

The main results obtained can be briefly summarized as follows: Thermal coagulation involves two stages, fast and slow. In the former, the necrosis domain grows quickly and its size attains values on the order of $\Re_{\lim}$ estimated by expression (23). The duration of this stage is about t_{cg} as determined by expression (24). The latter is characterized by a substantially slower growth of the necrosis domain. At this stage the temperature distribution in the tissue is quasi-stationary.

All through the course of treatment (except for a small area at its beginning), the temperature at the boundary of the necrosis domain remains approximately constant provided the tissue response to temperature variations is not delayed too long.

When the temperature response is strong enough, which gives rise to a substantial local increase in the blood perfusion rate, its distribution becomes extremely nonuniform. In this case in modeling thermal coagulation, one should take into account the fact that the temperature distribution is governed by the averaged blood perfusion rate rather than the true one.

The delay in the tissue response on time scales on the order of t_{cg} can significantly affect thermal coagulation. In this case, in particular, the duration of the fast stage is controlled by the delay time τ. The

Fig. 6 The temperature (curve 1) and the averaged perfusion rate (curve 2) at the necrosis interface Γ versus time for a tissue with a delayed response. Curve 3 shows the corresponding time dependence of the necrosis size $\Re(t)$. ($\tau=1.4$ min, $\epsilon=0.07$, $\lambda=0.5$).

limit size $\mathfrak{R}_{\text{lim}}$ attained by the necrosis domain under such conditions is determined by the initial value of the blood perfusion rate j_0 rather than values $(j_{\max} \gg j_0)$ near the necrosis domain at the second stage due to the tissue temperature response. In addition, in this case the second stage is characterized by even slower growth of the necrosis domain because the temperature decreases at its boundary. This is because such values of $\mathfrak{R}_{\text{lim}}$ could not be attained if the tissue response were immediate.

The form of the temperature distribution occurring in tissue during necrosis growth caused by thermal coagulation due to laser light absorption depends weakly on the particular values of physical parameters. The given property forms the basis for applying different variational techniques to an analysis of local thermal coagulation.

Models that deal directly with temperature distribution inside the layer of partially damaged tissue may be used to describe the necrosis growth caused by local thermal coagulation because the necrosis growth is not sensitive to particular regularities of heat propagation through this layer. Nevertheless, we think that it would be more consistent to use a free boundary model that regards the layer of partially damaged tissue as an infinitely thin interface of the necrosis domain.

Acknowledgments

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