JOURNAL OF BIOMEDICAL OPTICS 3(1), 102–111 (JANUARY 1998)

EFFECTIVE INTERFACE DYNAMICS OF LASER-INDUCED HEAT DIFFUSION-LIMITED THERMAL COAGULATION

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(Paper JBO-141 received Apr. 2, 1997; revised manuscript received Aug. 21, 1997; accepted for publication Aug. 24, 1991.)

ABSTRACT

The general problems of describing local thermal coagulation dynamics leading to the growth of necrosis that is limited by heat diffusion to surrounding live tissue is considered. It is demonstrated that in this case the typically used distributed model for thermal coagulation is based on a self-inconsistent approach, and a more rigorously justified free boundary model is derived. This free boundary model takes into account only the general properties of thermal coagulation and so provides a self-consistent description. It is shown that the two models, nevertheless, predict practically the same dynamics of necrosis growth because this growth is insensitive to the particular properties of heat transfer in the thin layer of partially damaged tissue. Necrosis growth is also simulated numerically under various physical conditions to verify the assumptions adopted.
 [S1083-3668(98)00501-2]

Keywords necrosis growth; laser-induced thermal coagulation; heat diffusion; bioheat equation; free boundary problem.

1 BACKGROUND

This paper provides a mathematical description of necrosis formation caused by local thermal coagulation of living tissue. In dealing with this problem we kept in mind the following physical model. Absorption of laser light delivered to a small internal region of living tissue causes the temperature to reach high values (about 70°C) that lead to immediate coagulation in this region. Heat diffusion into the surrounding live tissue causes its further thermal coagulation, giving rise to the growth of the necrosis domain. In this case heat diffusion plays a significant role in necrosis growth because the necrosis size $\mathfrak{R}$ exceeds the depth of laser light penetration into the tissue. Therefore the temperature distribution inevitably has to be substantially nonuniform, and for the tissue to coagulate at the peripheral points, the heat diffusion should cause the temperature to increase at these points. The latter property distinguishes the particular case of thermal coagulation discussed here from other possible types of thermotherapy treatment. That is why we refer to necrosis growth under these conditions as thermal coagulation limited by heat diffusion. We can estimate the typical duration t_{total} of such a treatment as $t_{\text{total}} \sim \mathfrak{R}^2/D$, where D is the temperature diffusivity of the tissue, and setting $\mathfrak{R}=5$ to 10 mm, $D=2\times10^{-3}$ cm^2/s gives $t_{\text{total}}\sim 2$ to 8 min. In a thermotherapy treatment based on shorter time regimes, heat diffusion seems not to play a significant role.

The effect of heat diffusion on local thermal coagulation has been considered and numerically simulated by a number of authors (see, e.g., Refs. 1 through 3 and the references therein). Leaving aside the description of laser light propagation in the tissue, we can generalize their models for necrosis formation to the following coupled equations for the temperature field $T(\mathbf{r},t)$ and the field $\zeta(\mathbf{r},t)$ determining the fraction of undamaged tissue at a given point $\mathbf{r}$ and time t:

$$c\rho\,\frac{\partial T}{\partial t}=\nabla(\kappa_{\text{eff}}\nabla T)-fc_b\rho_b j(T-T_a)+q, \qquad (1)$$

$$\frac{\partial \zeta}{\partial t}=-\zeta\omega(T). \qquad (2)$$

Here κ_{eff} is the effective thermal conductivity of the tissue; c, ρ, c_b, and ρ_b are the density and heat capacity of the tissue and blood, respectively; T_a is the temperature of blood in systemic arteries; j is the blood perfusion rate (the volume of blood flowing through a tissue region of unit volume per unit time), f is the factor accounting for the countercurrent effect;[4,5] q is the heat generation rate caused,

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for example, by absorption of the laser light, and $\omega(T)$ is the rate of tissue damage due to thermal coagulation.

The quantities κ_{eff} and f are the phenomenological parameters of the bioheat equation (1), with the factor f meeting the inequality $0<f<1$ and the effective thermal conductivity κ_{eff} being of the same order as the true thermal conductivity of the cellular tissue κ ($\kappa_{\text{eff}} \gtrsim \kappa$).[5] The rate $\omega(T)$ of tissue thermal damage depends strongly on T and for typical values of temperature attained during the treatment course can be approximated by the expression

$$\omega(T) = \omega_0 \exp\left\{\frac{T-T_0}{\Delta}\right\}. \tag{3}$$

Here $\omega_0 = \omega(T_0)$, where T_0 is a certain fixed temperature and Δ is a constant. It should be noted that expression (3) can be justified based on the available experimental data[6] for the temperature dependence of the exposure time or as an approximation of the Arrhenius dependence $\omega(T) \propto \exp\{-(E/T)\}$. In particular, these experimental data enable us to estimate the value of Δ as $\Delta \sim 3$ to 5°C ($\Delta \simeq 3.26$°C for pig liver at $T_0 = 65$°C). In what follows, the system of equations (1), (2), and expression (3) will be referred to as the ''distributed model'' for local thermal coagulation.

Let us consider the properties of local thermal coagulation that make the mathematical description of this process a nontrivial problem. During a typical course of thermotherapy treatment, high temperatures on the order of $T_{\max} \sim 100$°C are attained at the necrosis center, whereas at distant points, $T = T_a \approx 37$°C. Under such conditions, the damage rate $\omega(T)$ or, what is the same, the reciprocal value $t_{\text{cg}}(T) = 1/\omega(T)$, called the threshold exposure time of thermal coagulation, varies greatly in space (on scales of a necrosis size $\Re$). Indeed, at points where the temperature attains, for example, values of 60, 65, 70, and 75°C, the values of t_{cg} are 8 min, and 100, 20, and 5 s, respectively.[6] The typical duration t_{total} of the thermotherapy course is several minutes, which corresponds in order to the duration of the fast stage of necrosis growth[7,8] and $t_{\text{total}} \gtrsim \tau$. Here

$$\tau \overset{\text{def}}{=} \frac{1}{fJ} \sim 3 \text{ to } 6 \text{ min}, \tag{4}$$

is the characteristic time scale of the dynamics of necrosis growth and J is the mean value of the blood perfusion rate attained near the necrosis boundary.

In estimate (4) we used typical values of the blood perfusion rate $J \sim 0.3$, 0.5, and 0.7 min^{-1} for stomach, intestine, and spleen, respectively.[9] In addition, we have set $f = 0.5$, taking into account the experimental data[10] for the physical parameters of the bioheat equation (1) and the results of theoretical investigations.[12] So the layer in which thermal coagulation is under way at a given moment is characterized by a narrow temperature interval Δ in the vicinity of the coagulation temperature of $T_{\text{cg}} \sim 65$°C. This layer of partially damaged tissue separates the necrosis region ($\zeta \ll 1$) and live tissue ($\zeta \simeq 1$). Let us estimate the thickness δ_{pd} of this layer. As follows from the numerical analysis,[7,8] the temperature distribution is characterized by a single spatial scale, so in the necrosis domain the mean temperature gradient is about $\overline{\nabla T} \sim (T_{\max} - T_a)/\Re$. In addition, a necrosis size reaching typical values of 10 to 20 mm can be estimated as[7,8] $\Re \gtrsim \ell$, where

$$\ell \overset{\text{def}}{=} \sqrt{\frac{\kappa}{c\rho f J}} \sim 10 \text{ mm} \tag{5}$$

is the mean depth of heat penetration into the perfused tissue (here we also set $\kappa \sim 7 \times 10^{-3}$ W/cm·K, $c \sim 3.5$ J/g·K, and $\rho \sim 1$ g/cm^3). Then setting $\delta_{\text{pd}} \overline{\nabla T} \sim \Delta$ we get the desired estimate for the thickness of the layer of partially damaged tissue

$$\delta_{\text{pd}} \sim \frac{\Delta}{(T_{\max} - T_a)}\, l \sim 1 \text{ to } 2 \text{ mm}. \tag{6}$$

Therefore, to describe necrosis growth due to local thermal coagulation in the framework of the distributed model, one has to consider in detail the temperature field inside the layer of partially damaged tissue, which, on one hand, is thin enough and, on the other hand, directly governs necrosis growth. However, the distributed model describes the dynamics of local thermal coagulation in the context of the mean field theory. In other words, as soon as we deal with Eqs. (1) and (2), we make the underlying assumption that we convert from the microscopic equations governing heat exchange between cellular tissue and blood flowing through individual vessels to the mesoscopic description of this exchange in a certain effective continuous medium. This conversion is based on averaging the true temperature distribution in the tissue and the corresponding microscopic equations over spatial scales on the order of $\ell_{\text{av}} \sim \ell/\sqrt{L_n}$,[11,12] where $L_n = \ln(l/a)$, and l/a is the mean ratio of the individual lengths to the radii of blood vessels forming the peripheral system of blood circulation.[12] A typical value of the ratio $l/a \sim 40$ (Ref. 13) so $L_n \sim 4$. From this it follows that the temperature field $T(\mathbf{r},t)$ that appears in the equations of the distributed model may not have remarkable variations on spatial scales much less than the averaging scale ℓ_{av}. Thus, on these scales temperature nonuniformities cannot be rigorously described by the bio-

heat equation (1) and its validity is not obvious in cases where such temperature nonuniformities play a substantial role.

In addition, in the mean field approximation, we ignore the difference between the true temperature distribution in the tissue and the temperature field $T(\mathbf{r},t)$, i.e., we do not take into account the random component of temperature distribution caused by the discreteness of blood vessels. This is justified if the mean amplitude $\langle \delta T \rangle$ of such random nonuniformities of the tissue temperature is small. At the point where the averaged tissue temperature is equal to T, the value of $\langle \delta T \rangle$ can be estimated[12] as

$$\langle \delta T \rangle \lesssim \frac{1}{L_n}(T - T_a), \tag{7}$$

and taking into account other numerical constants, we get $\langle \delta T \rangle \sim (10 \text{ to } 20\%)\ (T - T_a)$ (see also Ref. 14).

Returning to the initial problem, we find from expression (6) that for the given values of parameters

$$\frac{\delta_{\mathrm{pd}}}{l_{\mathrm{av}}} \sim 0.2 \quad \text{and} \quad \frac{\langle \delta T \rangle|_{T=T_{\mathrm{cg}}}}{\Delta} \sim 1. \tag{8}$$

Therefore the distributed model for local thermal coagulation has to deal with spatial scales on which its basic equations are not rigorously justified.

Another problem following from the latter one is the specification of the main quantities characterizing the partially damaged tissue as a continuous medium that effectively approximates real cellular tissue with a vascular network embedded in it. Namely, we should specify the effective thermal conductivity κ_{eff} and the factor f as functions of the blood perfusion rate j and the fraction ζ of undamaged tissue:

$$\kappa_{\mathrm{eff}} = \kappa_{\mathrm{eff}}(\zeta, j), \quad f = f(\zeta, j). \tag{9}$$

However, these dependencies can be obtained only in the framework of the mean field theory discussed above and can adequately describe heat transfer only on scales about or greater than l_{av}. So we may write the corresponding relations only for live tissue where $\zeta \ll 1$. (Clearly, in the necrosis domain $\kappa_{\mathrm{eff}} = \kappa$, and we may set f equal to any value on the order of unity because $j = 0$ in this region.) In particular, it turns out[12] that at the first approximation $\kappa_{\mathrm{eff}} = F\kappa$, where the factor $F \gtrsim 1$ as well as $f \lesssim 1$ are certain constants specified by the vascular network architectonics.* Inside the layer of partially damaged tissue any dependence of the type $\kappa_{\mathrm{eff}} = \kappa_{\mathrm{eff}}(\zeta)$ or $f = f(\zeta)$ is nothing more than a formal phenomenological approximation of the actual complicated phenomenon. In particular, as follows from the results to be obtained in the next section, the details of the dependence $f = f(\zeta)$ are of no concern and below we will treat the value f as a constant.

In order to complete the description of the distributed model, we should describe how the blood perfusion rate depends on the fraction ζ of the undamaged tissue and the temperature distribution (the latter dependence is due to the tissue response to temperature variation). It has been proposed[2] to set

$$j(\zeta, T) = \zeta j_t(T), \tag{10}$$

where $j_t(T)$ is the perfusion rate that would occur in tissue without damage. Clearly, this is also a purely phenomenological approximation.

The only fact that could justify applying the distributed model to an analysis of local thermal coagulation is the independence of necrosis growth from particular details of heat transfer in the layer of partially damaged tissue. In this case, 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 motion of such an interface must be governed by the boundary values of the temperature and its gradient. Particular details of heat transfer in the given layer may be taken into consideration by a certain collection of parameters.

This paper attempts to show that this independence is really the case and to derive the corresponding free boundary model. In particular, formally assuming equation (1) to hold in the entire region under consideration, we reduce the system of Eqs. (1) and (2) to an equivalent free boundary model that deals with integrated characteristics of the tissue damage rate inside the layer of partially damaged tissue. In other words, the model aggregates the particular details of the functions $\kappa_{\mathrm{eff}}(\zeta)$ and $j(\zeta, T)$ to certain constants on the order of unity, which demonstrates the desired independence. It should be noted that in Ref. 15 we only presented initial results in developing this model.

2 EFFECTIVE INTERFACE DESCRIPTION OF NECROSIS GROWTH

In this section we derive the desired free boundary description of local coagulation assuming that Eqs. (1) and (2) hold at all the spatial points. The central point of the derivation procedure is to reduce the distributed model to equations dealing with the layer of partially damaged tissue in terms of an interface whose velocity is determined by local characteristics of the temperature field that do not vary

*It should be noted that, in general, the values F and f are functions of the blood perfusion rate j, which has been experimentally demonstrated in Ref. 10 by analyzing heat transfer in artificially perfused bovine tongues. However, due to the fractal structure of the vascular network, the functions $F(j)$ and $f(j)$ can be regarded as certain constants under typical conditions in living tissue.[12]

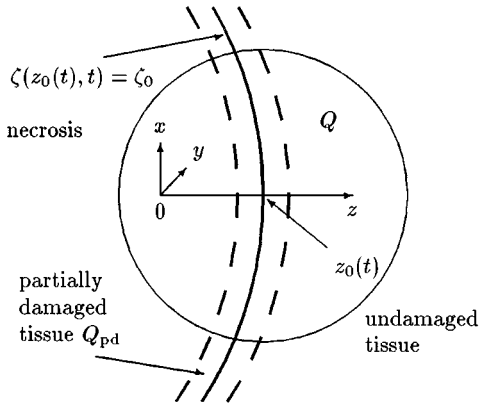

Fig. 1 The layer of partially damaged tissue and the local coordinate system.

over this layer and so remain unchanged at the nearest points of the living tissue and the necrosis region.

For the purpose of this section, it is sufficient to consider a specific neighborhood of a layer of partially damaged tissue. Let us choose the local coordinate system $\{\mathbf{r}:x,y,z\}$ as shown in Figure 1 and confine ourselves to the region Q crossed by the layer $Q_{\rm pd}$ of partially damaged tissue. The size of the region Q is assumed to be, on one hand, much smaller than the characteristic size $\Re$ of the necrosis domain and, on the other hand, much larger than the thickness $\delta_{\rm pd}$ of the layer $Q_{\rm pd}$. (In other words, we analyze the case when the tissue in the region directly affected by laser light has already coagulated.) So inside the region Q we may regard the layer $Q_{\rm pd}$ as a plane and treat the tissue temperature $T(z,t)$ as well as the fraction $\zeta(z,t)$ of undamaged tissue as functions of the coordinate z and the time t only, provided the z axis is locally normal to the layer $Q_{\rm pd}$.

In order to describe the dynamics of local thermal coagulation, we introduce the interface Γ specified by the condition

$$\zeta(\mathbf{r},t)\big|_{\mathbf{r}\in\Gamma}=\zeta_0, \tag{11}$$

where $\zeta_0\sim 0.5$ is a fixed value, and keep track of how it moves. Inside the region Q, the interface Γ may be regarded as a plane $z=z_0$, where the coordinate z_0 meets the equality $\zeta[z_0(t),t]=\zeta_0$ and the displacement of the point $z_0(t)$ as time goes on represents the motion of the interface Γ at the velocity $\vartheta_n=dz_0(t)/dt$.

In the given coordinate system, Eqs. (1) and (2) completed by expression (3) can be rewritten as

$$c\rho\,\frac{\partial T}{\partial t}=\kappa\,\frac{\partial}{\partial z}\left[\hat{F}(\zeta)\,\frac{\partial T}{\partial z}\right]-fc\rho j(T-T_a)+q, \tag{12}$$

$$\frac{\partial\zeta}{\partial t}=-\zeta\,\frac{1}{\tau}\exp\left\{\frac{T-T_0}{\Delta}\right\}. \tag{13}$$

Here the function $\hat{F}(\zeta)\sim 1$ is specified by the expression

$$\hat{F}(\zeta)=\frac{\kappa_{\rm eff}(\zeta)}{\kappa}, \tag{14}$$

where we have explicitly taken into account only the variable ζ because the other possible variables T and j_t in this expression can be regarded as constants inside the region Q. In addition, we have ignored the difference between $c\rho$ and $c_b\rho_b$ (or, what is the same, aggregated it into the value of f) and have chosen the temperature T_0 so that $\omega_0=1/\tau$. This is feasible because for typical conditions of thermotherapy treatment (see Sec. 1) the mean temperature $\hat{T}_{\rm pd}$ in the layer of partially damaged tissue meets the conditions

$$\hat{T}_{\rm pd}-T_a\gg\Delta \quad\text{and}\quad T_{\max}-\hat{T}_{\rm pd}\gg\Delta \tag{15}$$

so $\omega(T_a)\ll 1/\tau$ and $\omega(T_{\max})\gg 1/\tau$.

Let us now discuss the general features of the dynamics of the fields $T(z,t)$ and $\zeta(t,r)$. As mentioned in the previous section, necrosis growth as a whole is characterized by the temporal and spatial scales τ and l determined by expressions (4) and (5). In addition, temperature distribution in the vicinity of the necrosis domain is characterized by a single spatial scale.[7,8] Moreover, the form of the temperature distribution does not depend on the particular values of the tissue heat parameters but on their typical variations. Therefore we may set

$$\frac{\partial T}{\partial t}\sim\frac{T_{\max}-T_a}{\tau},\quad \frac{\partial T}{\partial z}\sim\frac{T_{\max}-T_a}{l},\quad\text{and}\quad \vartheta_n\sim\frac{l}{\tau} \tag{16}$$

as well as at the points belonging to the layer of partially damaged tissue

$$\frac{\partial\zeta}{\partial t}\sim\frac{1}{\tau}. \tag{17}$$

In addition, the mean value $\hat{q}$ of the heat generation rate at central points $r\lesssim\Re$ of the necrosis domain should meet the inequality

$$\frac{\hat{q}\,\tau}{c\rho(T_{\max}-T_a)}\lesssim 1 \tag{18}$$

and at distant points $r\gtrsim\Re$

$$\frac{\hat{q}\,\tau}{c\rho(T_{\max}-T_a)}\ll 1. \tag{19}$$

We note that it is the conditions (18) and (19) that actually allow us to regard the process of thermal coagulation as limited by heat diffusion.

At the next step of the derivation procedure we convert from the fields T and j to the corresponding dimensionless ones

$$\theta=\frac{T-T_a}{T_{\max}-T_a},\quad \eta=\frac{j}{\hat{j}}\sim 1, \tag{20}$$

and from the physical time t and the spatial coordinate z to the dimensionless variables

$$t'=\frac{t}{\tau}\quad\text{and}\quad x'=\frac{z-z_0(t)}{l\epsilon}, \tag{21}$$

where

$$\epsilon=\frac{\Delta}{T_{\max}-T_a}. \tag{22}$$

As follows from the estimates presented in Sec. 1, the value of ϵ is about 0.1 and it is the ratio ϵ that is treated as the small parameter required for reducing the distributed model to the free boundary one. It should be noted that this conversion from z to x' actually corresponds to measuring the spatial lengths in units of the thickness $\delta_{\rm pd}$ of the layer $Q_{\rm pd}$. Indeed, by virtue of Eq. (6) from (21) we get $z=z_0+x'\,\delta_{\rm pd}$.

In this section we will go to the limit $\epsilon\to 0$, fixing the value of

$$\theta_0=\frac{T_0-T_a}{T_{\max}-T_a}. \tag{23}$$

In other words, we will regard ϵ as a rather small parameter.

In terms of the given dimensionless variables, the system of Eqs. (12) and (13) can be represented in the form

$$\epsilon^2\,\frac{\partial\theta}{\partial t'}=\epsilon u\,\frac{\partial\theta}{\partial x'}+\frac{\partial}{\partial x'}\left(\hat{F}(\zeta)\,\frac{\partial\theta}{\partial x'}\right)+\epsilon^2(q'-\eta\theta), \tag{24}$$

$$\epsilon\,\frac{\partial\zeta}{\partial t'}=u\,\frac{\partial\zeta}{\partial x'}-\epsilon\zeta\,\exp\left\{\frac{\theta-\theta_0}{\epsilon}\right\}, \tag{25}$$

where we have introduced the dimensionless heat generation rate $q'(z,t)$ and the velocity u of the interface Γ by the expressions

$$q'=\frac{q\tau}{c\rho(T_{\max}-T_a)}\lesssim 1, \tag{26}$$

$$u=\frac{\tau}{l}\,\vartheta_n\sim 1 \tag{27}$$

and the given estimates follow from (16) to (19). In addition from (16) to (17) we get

$$\frac{\partial\theta}{\partial t'}\sim 1,\quad \frac{\partial\theta}{\partial x'}\sim\epsilon \tag{28}$$

and for $x\lesssim 1$

$$\frac{\partial\zeta}{\partial t'}\sim 1,\quad \frac{\partial\zeta}{\partial x'}\sim 1. \tag{29}$$

So at a lower order in the small parameter ϵ, the system of Eqs. (24) and (25) is equivalent to the following

$$\hat{F}(\zeta)\,\frac{\partial\theta}{\partial x'}=-\epsilon J_0(t'), \tag{30}$$

$$u\,\frac{\partial\zeta}{\partial x'}=\epsilon\zeta\,\exp\left\{\frac{\theta-\theta_0}{\epsilon}\right\}, \tag{31}$$

where $J_0(t')\sim 1$ is a function of the time t' only. It should be pointed out that the right-hand side of Eq. (31) is not small in spite of containing the factor ϵ. Indeed, the exponential factor, in turn, can be large for a small variation of the temperature θ in the layer $Q_{\rm pd}$ of partially damaged tissue. Moreover, from this it follows that for $x'\lesssim 1$

$$|\theta(\tilde{x}',t')-\theta_0(x',t')|\lesssim\frac{\epsilon}{\ln\epsilon}. \tag{32}$$

Dividing (31) by (30) and integrating the obtained equation, we get the solution specifying the field $\theta(\zeta)$ as a function of ζ

$$\frac{uJ_0}{\epsilon}\int_\zeta^1\frac{d\zeta'}{\hat{F}(\zeta')\zeta'}=\exp\left\{\frac{\theta(\zeta)-\theta_0}{\epsilon}\right\}. \tag{33}$$

In this way we have also taken into account that at distant points of the undamaged tissue, $x\gg 1$, the ratio $[\theta_0-\theta(\zeta)]/\epsilon$ must be great and $\zeta\simeq 1$. Setting $\zeta=\zeta_0$ and regarding the value of $\theta(\zeta_0)$ as the dimensionless coagulation temperature $\theta_{\rm cg}=\theta(\zeta_0)$, we obtain the desired relation between the dimensionless velocity u of the interface Γ and the characteristics of the temperature distribution:

$$u=\mathfrak{J}_0\,\frac{\epsilon}{J_0}\,\exp\left\{\frac{\theta_{\rm cg}-\theta_0}{\epsilon}\right\}, \tag{34}$$

where the constant $\mathfrak{J}_0\sim 1$ is specified by the expression

$$\frac{1}{\mathfrak{J}_0}=\int_{\zeta_0}^1\frac{d\zeta}{\hat{F}(\zeta)\zeta}. \tag{35}$$

Returning to the physical variables, we get from formula (34) the basic result, namely, the expression relating the velocity ϑ_n of the interface Γ, the value $T_{\rm cg}$ of the temperature at this interface, and the boundary value of the temperature gradient, for example, on the necrosis side $\nabla_n T|_{\Gamma-0}$:

$$\vartheta_n=\mathfrak{J}_0\,\frac{\Delta}{|\nabla_n T|_{\Gamma-0}}\,\omega_0\,\exp\left\{\frac{T_{\rm cg}-T_0}{\Delta}\right\}$$

$$= \Im_0 \frac{\Delta}{|\nabla_n T|_{\Gamma-0}} \omega(T_{cg}). \quad (36)$$

By virtue of (30) we also find that at a lower order in the small parameter ϵ, the heat flux has no sharp increase at the interface Γ, so

$$\kappa \nabla_n T|_{\Gamma-0} = \kappa_{eff} \nabla_n T|_{\Gamma+0} \quad (37)$$

[in the necrosis domain $\hat{F}(\zeta=0)=1$].

Expressions (36) and (37) are the essence of the free boundary model for the dynamics of local thermal coagulation and should lead to the same results as those predicted by the distributed model. Indeed, inside the necrosis domain where $\zeta \ll 1$, we may set $\zeta=0$ in Eq. (1) whereas inside the living tissue it is reasonable to set $\zeta=1$ in this bioheat equation. In both regions the characteristic spatial scales of temperature variations are about l and so the bioheat equation of the present form is well justified. In other words, let Q_n be the necrosis domain. Then for internal points $r \in Q_n$ we write

$$c\rho \frac{\partial T}{\partial t} = \kappa \nabla^2 T + q, \quad (38)$$

and for external points $r \notin Q_n$

$$c\rho \frac{\partial T}{\partial t} = \kappa_{eff} \nabla^2 T - f c_b \rho_b j (T - T_a) + q, \quad (39)$$

where κ_{eff} is the effective thermal conductivity of living tissue. This value, as well as the corresponding value of the factor f, can be directly obtained based on the regular procedure of averaging the microscopic equations for heat transfer. This equation leads to the same dynamics of the temperature field as the distributed model. Boundary conditions (36) and (37) join the temperature fields in the two regions, completing the description of necrosis growth in the frames of the free boundary model.

It should be pointed out that the free boundary model in its turn can be regarded as the initial point for modeling necrosis growth caused by local thermal coagulation. Indeed, all the information required for specifying the dependence $\vartheta_n(T)$ can be obtained from the experimental data for the temperature dependence of the threshold exposure time at a fixed temperature. The only parameter of this model that contains the particular information about the properties of heat transfer in the real layer of partially damaged tissue is the numeric factor $\Im_0$ of the order unity, $\Im_0 \sim 1$. Keeping the latter in mind, we may regard the analysis presented in this section as substantiation of the fact that necrosis growth caused by local thermal coagulation and limited by heat diffusion is insensitive to the particular details of heat transfer inside partially damaged tissue. Thus, it is justification of the distributed model rather than the free boundary model. Nevertheless, the results obtained indicate the particular form of the equations governing the dynamics of the necrosis interface that should be used in simulating local thermal coagulation.

To avoid misunderstanding, we note that the growth of the necrosis domain as a whole is certain to depend on the tissue thermal parameters. In addition, in general, the factor $\Im_0$ is a function of the blood perfusion rate j resulting from the dependence $F(j)$. However, because of the fractal structure of the vascular network, the function $\Im_0(j)$ can be regarded as a constant for typical variations of the tissue parameters.

Moreover, there is an additional reason to regard the free boundary model as the initial basis for simulating necrosis growth limited by heat diffusion. The fact is that we can obtain expression (36) at the semiquantitative level without using the distributed model at all and taking into account only the general properties of the tissue thermal coagulation. Indeed, let thermal coagulation be under way in a layer Q_{pd} at a given moment and the mean temperature and the mean temperature gradient inside this layer be T_{cg} and $\nabla_n T_{pd}$, respectively. Then the characteristic thickness δ_{pd} of the layer Q_{pd} can be estimated by the expression

$$\delta_{pd} \sim \frac{\Delta}{\nabla_n T_{pd}} \quad (40)$$

as has been demonstrated in Sec. 1. In fact, when necrosis growth due to thermal coagulation is limited by heat diffusion, the temperature distribution is substantially nonuniform in space. Therefore, on one hand, in the necrosis region, where the temperature exceeds T_{cg} by a value greater than Δ: $(T - T_{cg} > \Delta)$ and thus $\omega(T) \gg \omega(T_{cg})$, tissue coagulation has to be complete. On the other hand, in the region of undamaged tissue, the temperature is sufficiently low $[T_{cg} - T > \Delta$; and so, $\omega(T) \ll \omega(T_{cg})]$ so that the tissue does not have enough time to coagulate at such temperatures. Therefore tissue coagulation can be under way only in the region where $|T - T_{cg}| \lesssim \Delta$, from which we immediately get estimate (40).

After a lapse of the time interval $t_{thr} \sim 1/\omega(T_{cg})$, the tissue in the layer Q_{pd} has to coagulate practically completely. This is equivalent to the displacement of the layer Q_{pd} over the distance δ_{pd}. Thus, if we observe the points at which $\zeta \sim 0.5$, then we will see that these points move at the velocity

$$\vartheta \sim \frac{\delta_{pd}}{t_{thr}} \sim \frac{\Delta}{\nabla_{pd} T} \omega(T_{cg}). \quad (41)$$

Estimate (41) exactly coincides with expression (36) within a factor on the order of unity. Therefore the basic expression (36) of the free boundary model reflects the general properties of thermal coagulation rather than being directly related to the particular phenomenological approximations of the distributed model.

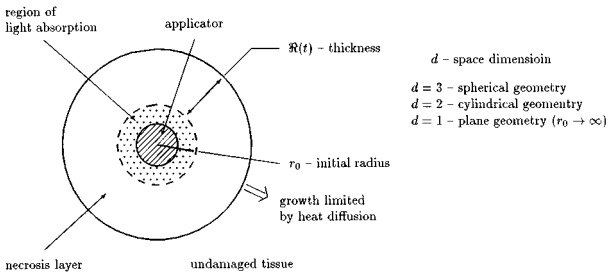

Fig. 2 The form of the necrosis region under consideration.

Beyond the present analysis, however, remains the basic question of whether the value Δ on the order of 3 to 5°C is small enough for the ratio ϵ to be regarded as a small parameter. This problem will be analyzed in the next section by numerically comparing the dynamics of necrosis growth predicted by the two models under various physical conditions.

3 MODEL USED IN THE NUMERICAL SIMULATION

We simulated necrosis growth in the tissue phantom shown in Figure 2. The applicator indicated by the dashed circle locally heats the tissue to high temperatures on the order of $T_b \sim 100$°C, which causes immediate tissue coagulation in the nearest neighborhood of the applicator (dotted region in Figure 2). This can be the case, for example, because of the direct heat exchange between the tissue and the applicator or irradiation by laser light and its absorption in an adjacent thin layer. The latter case corresponds to additional internal cooling of the applicator boundary, so the maximum T_b of the temperature attained just near the applicator does not depend on heat diffusion into the surrounding tissue. So keeping in mind possible vaporization control over the temperature maximum, we treat the value T_b as a boundary temperature fixed at the interface of a certain radius r_0. Generalizing both these situations, let us confine ourselves to the analysis of local coagulation assuming that:

At the initial time $t=0$ the necrosis region under consideration is a layer of zero thickness whose finite radius is r_0: $\zeta(r)=0$ and $T(r)=T_a \approx 37$°C for $r > r_0$.

The subsequent necrosis growth is governed solely by heat diffusion, i.e., we set $q(\mathbf{r},t)=0$ for $r>r_0$.

At the boundary $r=r_0$, the temperature is a fixed value: $T(r_0)=T_b \approx 100$°C.

At distant points the tissue temperature is equal to T_a: $T \to T_a$ as $r \to \infty$.

In other words, we confine ourselves to the region $r>r_0$ where the layer $r_0<r<r_0+\Re(t)$ of thickness $\Re(t)$ represents the necrosis domain whose growth is directly governed by heat diffusion only. The processes in the region $r<r_0$ are not considered. We ignore the real dynamics of initial coagulation in the immediate vicinity of the applicator boundary. The typical duration of the latter process can be estimated as $1/\omega(T_b)<1$ s for an applicator directly heating the surrounding tissue and as $\max\{1/\omega(T_b), q(r_0)/[c\rho(T_b-T_a)]\}$ for the laser applicator. In the present analysis this duration is regarded as a small parameter. Keeping in mind applicators of various forms, we studied necrosis growth in one-, two-, and three-dimensional tissue phantoms.

In order to also take into account the tissue response to temperature variations, we should describe the dynamics of the blood perfusion rate $j(\mathbf{r},t)$. This response is due to the expansion of blood vessels as the temperature grows. As shown in Refs. 12, 16, and 17, at least as the first approximation, this tissue response obeys the following local equation relating the blood perfusion rate $j(\mathbf{r},t)$ and the tissue temperature $T(\mathbf{r},t)$ taken at the same point $\mathbf{r}$:

$$\tau_{\mathrm{del}} \frac{\partial j}{\partial t} + j\Phi(T) = j_0 . \tag{42}$$

Here j_0 is the blood perfusion rate under normal conditions, τ_{del} is the delay time of the tissue response, and the function $\Phi(T)$ is of the form

$$\Phi(T) = \begin{cases} \alpha + (1-\alpha)\dfrac{T_{\mathrm{vr}}-T}{T_{\mathrm{vr}}-T_a} & \text{for } T<T_{\mathrm{vr}} \\ \alpha & \text{for } T>T_{\mathrm{vr}} \end{cases}, \tag{43}$$

where $\alpha = j_0/j_{\max}$ is the ratio of j_0 and the maximum $j_{\max}$ of the blood perfusion rate that can be attained in living tissue from vessel expansion caused by a temperature increase, and $T_{\mathrm{vr}} \approx 45$ to 46 °C is the temperature at which the blood vessels exhaust their ability to expand. It should be noted that the tissue response to local temperature variations is sufficiently strong that the blood perfusion rate can locally increase by tenfold.[18]

In the next section we present the results for the dynamics of necrosis growth obtained numerically for the following typical values of the main tissue parameters: $\kappa \sim 7\times10^{-3}$ W/cm·K, $c \sim 3.5$ J/g·K, $\rho \sim 1$ g/cm^3, and $j_0 \sim 0.3$ min^{-1}. We also have set the constants $F=2$ and $f=0.5$. By the corresponding renormalization, the above-stated models can be reduced to the dimensionless form. In particular we have converted from t and r to the dimensionless variables t' and r' such as $t=\tau_0 t'$ and $r=l_0 r'$, where

$$\tau_0 = \frac{1}{fj_0} \quad \text{and} \quad l_0 = \sqrt{\frac{\kappa}{c\rho f j_0}},$$

and in obtaining the results to be presented we have set $\tau_0 = 6$ min and $l_0 = 10$ mm for the given val-

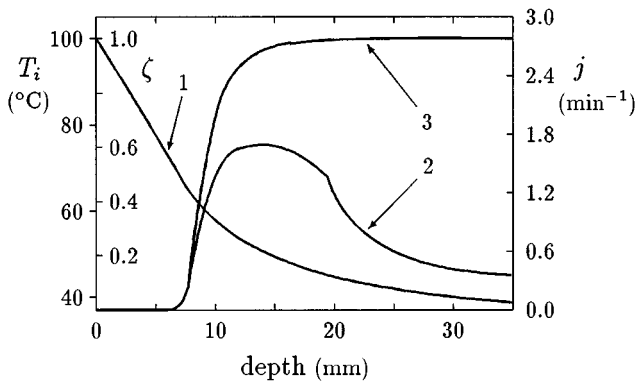

Fig. 3 The typical form of the spatial distribution of the tissue temperature (curve 1), blood perfusion rate (curve 2), and fraction of undamaged tissue (curve 3). (In obtaining the curves we set $j_{max}=10\ j_0$ and $\tau_{del}\approx 1$ min and considered a one-dimensional tissue phantom.)

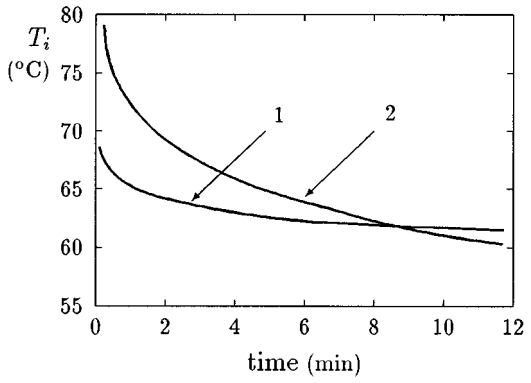

Fig. 4 The time dependence of the temperature T_i at the point r_i where $\zeta(r_i)=0.5$ for different values of the parameter Δ. (Curves 1 and 2 correspond to $\Delta=1.5$°C and $\Delta=5.0$°C, respectively. In obtaining the curves we considered a one-dimensional phantom of the tissue without response to temperature variation.)

ues of these parameters. We will compare the dynamics of necrosis growth, namely, the time dependence of the thickness $\Re(t)$ of the necrosis layer and the coagulation temperature $T_{cg}(t)$ predicted by the free boundary model with that given by the distributed model. In the latter case we have used expression (10) and specified the required dependence of the effective thermal conductivity κ_{eff} on the fraction ζ of undamaged tissue by the function $\hat{F}(\zeta)=(F-1)\zeta+1$. In addition, for the distributed mode, the necrosis interface Γ has been specified by the condition $\zeta|_{r\in\Gamma}=0.5$. The temperature dependence $\omega(T)$ (where T is in degrees Celsius) has been taken in the form

$$\omega(T)=0.2\times\exp\left[\frac{T-60}{3.6}\right]\quad(1/\text{min}),\qquad(44)$$

which corresponds to the available experimental data for the threshold exposure time t_{thr} (in seconds) required of tissue coagulation under a fixed temperature.[6]

4 DYNAMICS OF NECROSIS GROWTH

In Figure 3 we demonstrate the typical form of the temperature distribution $T(r)$, the distribution of the fraction $\zeta(r)$ of undamaged tissue, and the blood perfusion rate $j(r)$ obtained for a one-dimensional tissue phantom in the frames of the distributed model. As seen in Figure 3, the region in which the fraction ζ of undamaged tissue varies substantially in space is small. So on spatial scales characterizing the temperature decrease, such an increase in the value $\zeta(r)$ may be treated as a sharp jump. The latter actually justifies using the free boundary model for the given values of the physical parameters, namely, assigning to an effective necrosis boundary a certain coagulation temperature T_{cg} and certain values (on both sides) of the temperature gradient.

Figure 4 illustrates another characteristic of local thermal coagulation. The free boundary approximation is rigorously justified provided the temperature distribution inside the layer of partially damaged tissue can be regarded as quasi-stationary. The latter is the case when, in particular, the time variations $\delta_t T_{cg}$ of the coagulation temperature T_{cg} are small during necrosis growth, which in mathematical terms may be stated as the condition $\delta_t T_{cg}\to 0$ as $\Delta\to 0$. Figure 4 demonstrates that this condition may be fulfilled. Indeed, the smaller the parameter Δ of the tissue damage rate $\omega(T,\Delta)$, the more the time variations of the coagulation temperature T_{cg} are smothered, except for a short initial period of necrosis growth. In addition, this feature of local thermal coagulation justifies, at least at the qualitative level, the model proposed in our previous papers,[7,8] which considers the coagulation temperature T_{cg} as fixed during necrosis growth.

Figure 5 demonstrates the fact that the distributed model [(1) and (2)] leads to the same dynamics of necrosis growth as that predicted by the free boundary model [Eqs. (36) through (39)] for one-, two-, and three-dimensional tissue phantoms [Figures 5(a,b), 5(c,d), and 5(e,f), respectively].

These results have been obtained for a tissue phantom with a strong ($j_{max}=10\ j_0$) and delayed ($\tau_{del}=2$ min) response to temperature variations and so provide in themselves the characteristic features of necrosis growth in tissue without a response as well as with a strong immediate response.

The results not only clearly show that the particular details of thermal coagulation in a partially damaged layer are not a relevant factor but also indicate that the value of ϵ for $\theta\approx 3$ to 5°C can be treated as a small parameter of perturbation theory.

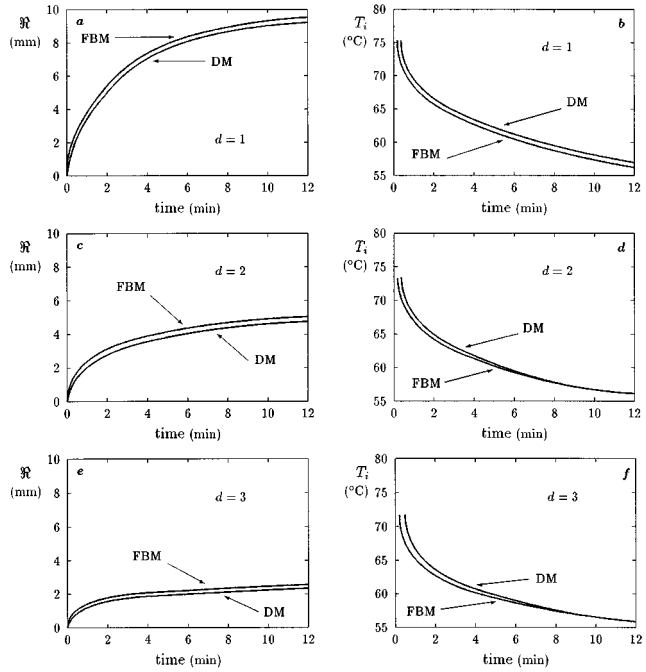

Fig. 5 Comparison of necrosis growth predicted by the distributed model (DM) and the free boundary model (FBM). The thickness $\Re(t)$ of the necrosis layer and the temperature $T_i(t)$ at the necrosis interface are plotted against time t for heat sources of (a,b) the plane, (c,d) cylindrical, and (e,f) spherical forms. (In numerical calculations we set $\tau = 2$ min and $j_{max} = 10\, j_0$. For the distributed model, the value T_i is specified as $T(r_i)$ at the point r_i at which $\zeta(r_i) = 0.5$.)

So the two models may be treated as equivalent, but the free boundary one does not contain self-inconsistent elements. In addition, the free boundary model can be used to construct a faster numerical algorithm for simulating necrosis growth because in this model we need not consider the thin layer of partially damaged tissue. So in this case we may deal with the partition of the temperature field only in the necrosis region and the region of undamaged tissue where the temperature is smooth enough.

5 CONCLUSION

In this paper we have shown that:

- Necrosis growth caused by heat diffusion-limited thermal coagulation depends only weakly on the particular details of heat transfer inside the region of partially damaged tissue (Sec. 2).
- The region of partially damaged tissue is a thin layer, $\delta_\zeta \sim 1$ mm (Sec. 1), and so the dynamics of necrosis growth can be described in terms of a certain interface moving in space. Its motion is governed by the tissue temperature at this interface and the boundary value of the temperature gradient (Sec. 2).
- Although the mean field models (similar to the distributed model) dealing with the averaged tissue temperature (i.e., ignoring random temperature nonuniformities due to the vessel's discreteness) do not hold on scales on the order of δ_ζ (Sec. 1), they can be used in modeling local thermal coagulation (Secs. 3, 4).

Based on the results obtained, we have proposed a new mathematical model for necrosis growth caused by heat diffusion-limited thermal coagulation. This model:

- regards the layer of partially damaged tissue as a layer of infinitely small thickness, the motion of which is governed by the boundary values of the temperature and its gradient; it thereby provides a self-consistent description of heat transfer in living tissue for modeling local thermal coagulation;
- singles out the characteristic features governing the dynamics of the necrosis growth; and
- can be the basis of a faster numerical algorithm for simulating necrosis growth because the free boundary model deals only with the regions where the temperature distribution $T(\mathbf{r},t)$ is a smooth field.

Acknowledgments

This research was supported in part by the International Science Foundation, Grant U1I200, and the Russian Foundation of Basic Research, Grants 96-02-17576 and 96-15-97782.

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